Federal Agency Roles in Cancer Drug Development from Preclinical Research to New Drug Approval: The National Cancer Institute and the Food and Drug Administration

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FEDERAL AGENCY ROLES IN CANCER DRUG DEVELOPMENT FROM PRECLINICAL RESEARCH TO NEW DRUG APPROVAL:

THE NATIONAL CANCER INSTITUTE AND THE FOOD AND DRUG ADMINISTRATION

Background paper prepared for the National Cancer Policy Board

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Willing is not enough; we must do."
—Goethe

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PREFACE

The interplay between the public and private sectors in health care is nowhere more intricate than in the case of cancer. From basic research to the panoply of control measures, to the subject of this background paper—the development of new drugs and biological agents to treat the disease most feared by Americans—the leading federal government agencies have played essential roles. The Food and Drug Administration (FDA) is an obvious player, responsible for expediting the flow of new agents for the full range of health conditions to the public, while protecting from undue risk. Challenges for FDA abound throughout the medical spectrum, but cancer occupies a special place, with rules and procedures peculiar to the disease, its treatment, and the public's clamor for faster progress.

It should surprise no one that the National Cancer Institute (NCI) is at the forefront of basic research on cancer, but the historic and current depth of the Institute's involvement in drug development is an anomaly among the government's disease-oriented institutes. Its role in relation to the traditional pharmaceutical industry, small and large biotechnology companies, and the academic community has been central since the 1940s, but has changed over time as the capacity and priorities of the other parties have evolved. Continued success will depend on the flexibility to fully complement the other sectors with cutting-edge technical capabilities as well as having in place the administrative means to join easily with them throughout the discovery and development process.

These issues were part of the very ambitious scope of work of a committee created under the aegis of the National Cancer Policy Board to analyze every aspect of the way new agents to fight cancer are developed and to search for ways to streamline the process. This scope was overwhelming, and it became clear that shorter reports, a typical committee report and three separate authored papers on various aspects of the process, would be more manageable and provide more accessible products. This authored background paper, describing the federal role in cancer drug development, is one of those. The other products from this study are a committee report on the development of agents to treat childhood cancers and two authored background papers covering the use of human tissues in research to develop new anticancer agents and issues in intellectual property among government, industry, and academia.

We believe this paper provides useful background detail for those interested in exploring issues that will be informed by how the FDA and NCI act and interact to develop cancer drugs from preclinical research to new drug approval.

Joseph P. Newhouse, Ph.D.

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SCIENTIFIC RATIONALE

Introduction

The National Cancer Institute (NCI), since it began work in the 1930s, has played a central role in cancer research worldwide, including the research and development enterprise for new cancer drugs in the United States. Pharmaceutical companies were reluctant to enter the oncology market until the drugs developed by NCI began to demonstrate that cancer was, in fact, treatable and, in some cases, curable, although they played their usual roles in producing and marketing cancer drugs developed by NCI. Today, even though a few large pharmaceutical companies and a host of smaller pharmaceutical and biotechnology companies are engaged in cancer drug development, the role of the NCI remains large, commensurate with its current $4-5 billion annual budget (see NCI section below).

Over much of the same span of time, the Food and Drug Administration (FDA) has been responsible for approving anticancer drugs and (later) biologics, for safety and efficacy. With advances in cancer science and commensurate advances in cancer treatment, the FDA's contributions to standards for preclinical and clinical testing and approval of therapeutics for cancer patients have grown. Encouraged by the promise of new cancer therapies (and to some extent by external influences), the agency has sharpened its focus on cancer organizationally as well as scientifically (see FDA chapter below).

Prior to the identification of cancer genes (oncogenes), tumor suppressors, and other factors that act in complex molecular pathways to control cell physiology and proliferation, cancer drug discovery occurred in at least three important ways. It could be fortuitous, stemming from unexpected findings in the course of studies not directed toward controlling the disease; it was often highly empirical, relying on the screening of large numbers of compounds and complex biochemical extracts derived at random (or nearly so) from myriad synthetic, microbial, botanical, marine, and other sources; or it was grounded in concepts of cell cycle, drug resistance, and biochemical pharmacology before such efforts shifted to seeking agents that blocked key molecular pathways that had been identified as causing cancer (Chabner and Roberts, 2005).

These approaches have uncovered many effective anticancer agents that form the core of contemporary chemotherapy. However, most of these agents have significant adverse side effects that cannot easily be eliminated without decreasing therapeutic effectiveness because, while they may have a high affinity for cancer cells, they do not target vulnerabilities unique to cancer cells. Consequently, the development of a promising lead compound into a therapeutic agent that is safe, effective, and has tolerable side effects is typically a slow and expensive process, and most of the time and resources spent during this process yield little of value because the majority of lead compound derivatives fall by the wayside before they ever reach the clinic.

Today, with the complete mouse and human genome sequences in hand, and an increasingly sophisticated view of the molecular and cellular biology of cancer at the disposal of researchers, we are poised to enter an era of rational cancer drug development in which the targets of promising therapies, and the methods for hitting these targets, are more readily identifiable than ever before. Scientists in government, industry, academia, and non-profit research institutes—working independently and collaboratively—have already used the human genome sequences to pinpoint several new genes that are deleted or amplified in human cancers, or that are aberrantly switched on or off in cancer cells (Sherwood, 2003).

Approaches to Cancer Drug Discovery

Concerted efforts to find effective anticancer agents began after World War II, following observations that personnel exposed to mustard gas during World War I had experienced severe bone marrow depression, and that this feature of mustard gas derivatives was a dominant theme in molecules synthesized through the World War II era. Nitrogen mustard was subsequently found to display significant effects against lymphoma and became a starting point for the synthesis of many related drugs that damage DNA and, as a result, are preferentially toxic to proliferating cells.

The therapeutic successes of these drugs, called alkylating agents, were paralleled by similar postwar outcomes with other drugs, called antimetabolites. These compounds interfere with DNA synthesis and hence disrupt cell proliferation by inhibiting the production of the building blocks of DNA.

In 1956, Bristol Laboratories contracted with the NCI to identify potential anticancer antibiotics and formed a similar research alliance with Japanese researchers. This work led to the discovery of a number of anticancer antibiotics. Other important examples were discovered by Italian researchers.

Many chemotherapy agents were later derived from plant sources, some from the extensive NCI natural products screening program which was discontinued in 1982, and others from a new natural products program begun in 1986, which produced a number of drugs from marine sources.

Clearly, the compounds that emerged from the empirical approaches to cancer drug discovery act through specific pathways—molecular pathways—even though they were not selected or developed with precise foreknowledge of the targets or processes that they would be affecting. Empirical drug discovery still continues, but there is a shift toward using the detailed information emerging from basic research about the molecular abnormalities that underlie cancers and the peculiarities of cancer cells to look for agents with specificity for those targets.

The first hints that cancer patients could be restored to health by modulating a specific biological process emerged from studies of the hormonal control of prostate tumors in the 1940s at the University of Chicago. The large-scale transition of cancer drug discovery that continues to evolve was made possible by numerous subsequent lines

of inquiry—many with origins in basic research funded by the NIH in the late 1960s and early 1970s which explored the biology not only of human cells, but also of other seemingly unlikely yet ultimately telling cellular sources. This work, carried out primarily at universities and non-profit research institutes, revealed the fundamental mechanisms of growth control and programmed cell death and led to the identification of a large number of molecules and pathways that regulate the proliferation of cells of higher animals. These findings eventually enabled researchers directly interested in cancer to pinpoint promising molecular targets and growth control pathways for the development of novel cancer therapies.

The discovery in the late 1970s and early 1980s of the cellular cancer genes (oncogenes) and later of tumor suppressor genes spawned the detailed molecular description of cancer that now prevails and helped explain the root causes of cancer. A landmark publication by Hanahan and Weinberg (Hanahan and Weinberg, 2000) outlines six "hallmarks of cancer" (to which evading immune system surveillance and impairment of DNA repair might be added), all of which have known molecular components that are being investigated as therapeutic targets.

The Hallmarks of Cancer as Targets for Therapy

According to Hanahan and Weinberg, the complexities of cancer physiology revealed over the past three decades can be understood in terms of a small number of underlying principles, or hallmarks, of cancer. One hallmark of cancer cells is their escape from control of extracellular growth factor signals. Instead, owing to mutations or overactivity in growth factor receptors or any of a number of other signal transduction components or transcription factors, cancer cells generate their own growth signals. They therefore, can grow independently. Today, small molecules and monoclonal antibodies that target aberrant growth factor signals or receptors are prominent examples of targeted cancer therapies aimed at this kind of abnormality.

To maintain the integrity of tissues (such that they comprise neither too many nor too few cells) and to guide the differentiation of cells into specialized types, several antiproliferative "don't grow" signals operate within and between cells, which either may cause cells to permanently exit the cell division cycle and adopt specialized properties, or alternatively divert cells from the cell division cycle and lead them into a quiescent state from which they may resume proliferating if future conditions dictate. In normal cells, anti-growth signals are relayed in large part by a pathway that is controlled by a prototypical tumor suppressor protein. A second hallmark of cancer is the loss of this suppressor function in cancer cells which can lead, for example, to the unopposed activation of a powerful growth stimulating transcription factor. This factor is a promising target for attack by small molecule drugs under development.

A third hallmark of cancer is disruption of the normal cellular process of programmed cell death (apoptosis). Surplus cells in developing or adult organisms receive extracellular signals to kill themselves, and pre-cancerous cells can detect that they are abnormal and similarly commit suicide through this process. Disruption of programmed cell death through mutations in tumor suppressor genes or increased levels

of activity of inhibitors of the process allows cancer cells to survive and proliferate. Treatments under investigation to address these abnormalities are aimed at targeting the changes in cellular mechanisms that result from defective tumor suppressor genes or overactive inhibitors of programmed cell death, among others.

A fourth hallmark of cancer relates to the normal process in which the tips of chromosomes in most human cells become progressively shorter in each cycle of cell proliferation. With the exception of stem cells (which can proliferate indefinitely), normal human cell types, after 60 or 70 doublings, sense that their chromosome tips have become too short to support additional cell division without compromising chromosome integrity, and they either cease proliferating or die. In stem cells and in cancer cells, an enzyme actively maintains the DNA sequences located at the tips of chromosomes, and provides stem cells and cancer cells limitless replicative potential. One strategy for cancer therapy involves the development of inhibitors of the enzyme which would block the capacity for endless proliferation of cancer cells.

Another hallmark of cancer involves the ability of tumors to capture the usually tightly regulated process of new blood vessel formation (angiogenesis), and, in so doing, to provide themselves with increasing supplies of oxygen and nutrients as they grow. Cutting off the blood supply to tumors by blocking this process with various inhibitors has therefore emerged as a promising cancer therapy.

Metastasis, or the ability to develop pioneer cells that leave the primary tumor and invade distant tissues, is a sixth, and deadly, hallmark of cancer, accounting for 90 percent of cancer deaths. Tissue invasion and metastasis by cancer cells involve the severing of normal linkages between cells and their intercellular matrix. The activation of extracellular protease enzymes enables migrating cancer cells to slip through the normally impassable spaces between cells in tissues and blood vessel walls. Blocking tissue invasion and metastasis is predicted to significantly improve the prognosis of cancer patients. However, these processes are arguably the least well understood among the prominent hallmarks of cancer, and progress in developing therapies directed against the molecules involved in tissue invasion and metastasis has been slow.

Advances in Cancer Science and Drug Development

The complete human genome sequences provide new opportunities for discovering genes altered in cancer cells or expressed at significantly increased or decreased levels. Moreover, by grouping numbers of genes—some with known and others with unknown functions—into co-regulated sets, researchers can obtain clues to the function of previously uncharacterized genes. Other analyses reveal which few genes are the linchpins of a particular process in tumors, how they are functionally related to each other, and what approaches might be taken toward developing therapies based on this information.

These advances have become the basis in preclinical research for a variety of high-throughput screens to identify candidate targets for drugs; for determining the extent to which lead compounds affect the molecular pathways of interest; and for

characterizing potential adverse side effects of agents under development by determining whether the agents affect a molecular pathway or pathways associated with adverse side effects. Much of the past progress and future discovery of the kind outlined above has come about since the advent of DNA microarray analysis (which can analyze the expression of thousands of genes in a cancer sample) and related technologies that continue to be developed (Clarke et al., 2001).

Identification of the many individual proteins in large multiprotein complexes and determining the functional relationships among these proteins and how such protein complexes are altered in cancer cells or in response to therapy, that is, proteomics, has resulted from technological advances in protein mass spectrometry and from the marriage of this technology to complete genome sequence information. Accordingly, results that previously required years of effort to obtain (that is, by the cloning and sequencing of the genes encoding such large numbers of proteins) now take only days or weeks, and such results provide researchers valuable information much more rapidly than traditional methods for establishing functional relationships among proteins (Petricoin et al., 2004).

Progress in both genomics and proteomics research has been spurred by parallel developments in a blend of molecular biology and computer science called bioinformatics. Biologists, programmers, and others engaged in bioinformatics research are developing increasingly sophisticated analytical software, powerful statistical methods, databases, and user interfaces for the management, manipulation, and mining of experimental genomic and proteomic data and other allied information (such as human knowledge and the vast amount of published information about a particular topic). The organization and analysis of large amounts of experimental data and other biological information is crucial for enabling researchers to explore the landscape of the human genome and proteome, reveal new sequence elements within DNA or functional domains within proteins, and correlate these features with cancer biology.

To identify or validate therapeutic targets, and to assess drug efficacy and toxicity in cell culture or in animal models, researchers may employ animals with precisely-defined genetic backgrounds, including the absence of a particular relevant gene – a gene knockout. Using new tcchnology, called RNA interference, scientists can reliably create these knockouts in a wide variety of organisms from mice and other mammals to fungi, fruit flies, and plants in a stably inherited form, and thus examine experimental animals without a gene (and function) of interest under a variety of experimental conditions. A knockout shows researchers what would happen if an agent against that target were completely effective.

Cancer immunotherapy is an approach to treating the disease or preventing recurrences by encouraging the immune system to recognize cancer cells as foreign and attack them. New insights into the cells, molecules, and signaling pathways that regulate immune responsiveness are reinvigorating this field (Pardoll, 2002). Overall, one can conclude that tumors that reach the stage of being clinically detectable are likely to have done so either by generating tolerance in the immune system or by developing ways of resisting immune recognition. In terms of cancer treatment, immunotherapeutic

approaches are geared toward identifying ways to break tolerance or circumvent resistance mechanisms.

Recently, research has been focusing on designing antibodies to act on cell types and molecules necessary for tumor growth and on using antibodies as vehicles to carry a toxic agent to a tumor site (Dillman, 2001). Numerous approaches to cancer vaccines are also being tested (Fearon et al., 1990, Pardoll, 2002a), and the future may see more widespread use of immunotherapy in combination with other modalities: surgery plus radiation plus immunotherapy, for example. However, a major challenge in cancer vaccines remains finding strategies to break self tolerance and generate immunity through manipulating both the vaccine target (antigen) and the delivery system (Wang and Wang, 2002).

Summing Up Cancer Science

The increasingly rapid identification of specific therapeutic targets—as outlined above—and improvements in validating these targets through refined *in vitro* systems and more sophisticated animal models of cancer provide an important foundation for developing small molecules and other agents with the potential to be highly specific, potent, and non-toxic. And immunologic approaches are zeroing in on ways to engage the immune system very specifically against cancers.

The future development of successful agents will involve both traditional and modified high-throughput screening of very large combinatorial libraries of compounds as well as *in silico* molecular modeling (so-called "rational drug design"), both of which will be supported by improved and accelerated methods for determining structure-activity relationships of drug candidates.

Progress in every stage of cancer drug discovery and therapy— from target identification, to compound development, to rational treatment regimens based on precise molecular diagnoses of individual patients—is poised to provide the next generation of cancer patients, and certainly the generation after that, with far better options for eliminating or controlling their disease than exist today. The next chapters of this background paper discuss the programs of two key federal agencies for realizing those better options for cancer drug development.

2

THE NATIONAL CANCER INSTITUTE

Introduction

The National Cancer Institute (NCI) has been involved in the discovery and development of many of the anticancer agents currently in use. At $50 billion in public funding over the past 30 years, it has been the largest such public investment in the world and one that is without parallel in any other therapeutic area. A guiding principle of NCI activities related to drug development has been that they must complement industrial efforts, and the goal has been to expedite the best molecules for cancer treatment from discovery into clinical trials (Monks et al., 1997).

NCI was the early leader in discovery and development of cancer drugs (short of production and marketing), but in the past few decades, the private sector has invested substantially in bringing new drugs to market, although it is still highly dependent on discoveries from NCI-supported research. NCI's challenge is to complete the transition from the dominant or sole force to a complementary role that leverages the public resources that it commands to best advantage, as well as remaining a leader in new approaches to, and the underlying basic science for, drug development.

History

In 1944, the Public Health Service Act made NCI a division of the Public Health Service's National Institute of Health (NIH) with the intent of encouraging NCI research. The American Society for the Control of Cancer also reorganized itself in 1944, becoming the American Cancer Society, and continuing to work in cooperation with NCI on research and educational activities (American Cancer Society, 2004).

When the NIH clinical center opened on the Bethesda, Maryland campus in 1953, clinical research projects in cancer were transferred to the center. However, grants for extramural research continued, particularly in the growing area of chemotherapy. In 1955, uncertain about industry interest or academic capacity and dissatisfied with NCI's lack of direct involvement in drug discovery (Sausville and Feigal, 1994; Zubrod, 1984), Congress appropriated funds to NCI for a national drug development effort, the NCI National Chemotherapy Program.

Accordingly, the Cancer Chemotherapy National Service Center (CCNSC) was formed, primarily as an extramural program, with all of the functions of a pharmaceutical house run by NCI and operations dispersed in industry and academic institutions (Zubrod, 1984). With a 1955 budget of $5 million, initial contracts were let to four screening centers operating through the CCNSC (Zubrod et al., 1977). By the mid 1960s, the CCNSC had combined its intramural and extramural activities in drug development.

Also during this time, with another $5 million from Congress, NCI initiated the cooperative group model for testing chemotherapeutic agents in clinical studies. By 1958,

17 groups had been formed. The Eastern Cooperative Group, the first of the cooperative groups, carried out a trial comparing two drugs in breast cancer, Hodgkin's disease, and melanoma that was designed by an NCI Clinical Panel. The Panel also assessed the early principles of clinical trials in cancer chemotherapy and reviewed trial data coming from an emerging number of cooperative groups around the country (Zubrod, 1984). This was the first active, prospective involvement of NCI in large-scale cancer clinical trials.

In 1976, the CCNSC was incorporated into NCI's Developmental Therapeutics Program (DTP), the current locus of federally funded preclinical drug discovery and development. The heart of DTP was to become a large-scale *in vivo* drug screening operation that, by the late 1970s, tested up to 40,000 compounds per year in a variety of mouse leukemia models (Chabner, 1990). More than 500,000 chemicals were tested in laboratory animals in this program, and several hundred were tested in clinical trials. By the late 1970s, some 45 chemicals had been found effective in various cancers. Overall, DTP has had a role in the discovery or development of approximately 40 percent of the current U.S.-licensed chemotherapeutic agents (Sausville and Feigal, 1999), with the rest coming directly from the domestic or international pharmaceutical industry.

Evolving Screening Approaches

Preclinical models used by NCI to select new drugs for cancer clinical trials have evolved over time due to improved understanding of the biologic factors that affect the success of treatment, such as the relationship of tumor cell growth kinetics to drug responsiveness, to retrospective analyses of correlations between clinical and preclinical efficacy, and to the development of the NCI Drug Information System, a computer inventory of compound structure and activity in the mouse models, that limits the screening of analogues and directs the focus to novel structures (Schabel, 1969; Skipper et al., 1970. Venditti, 1981, Venditti et al., 1984).

In the 1940s, the S37 tumor was used to screen 300 chemicals and plant extracts, but by 1955 mouse leukemia models were selected as the initial systems for large-scale screening because they were relatively inexpensive and allowed for high throughput of compounds (Monks et al., 1997; Vendetti, 1981, Venditti et al., 1984, Zubrod, 1984). From its inception, therefore, until the mid 1970s the mouse screen would be used to process more than 400,000 compounds (Khleif and Curt, 2000). There are examples where this appeared to predict well for the clinic, but there was concern that screening against animal leukemia may have created a bias toward drugs that were active only against rapidly growing tumors. While treatment of human leukemias and lymphomas had improved during this period, lesser improvements in the chemotherapy of most human solid tumors were achieved (Venditti, 1981, Venditti et al., 1984).

The 1970s

In the 1970s, the availability of the athymic nude mouse, a model with a defective immune system that accepted transplanted foreign (non-mouse) tumors (Giovanella et al., 1974), permitted inclusion of human tumor grafts in a screening panel to identify agents in addition to those selected by mouse tumor screens. Candidate agents were screened

against matched pairs of animal and human tumors from the same organ site to determine if tumor origin was a factor in drug selection (Venditti et al, 1984). To limit the number of compounds tested through this more complex approach, NCI used a relatively sensitive and cost-efficient *in vivo* prescreen -- a specific mouse leukemia that was sensitive to most classes of clinically effective drugs -- and the criteria for activity in this model were set low (Venditti et al., 1984). The panel of tumors against which selected materials was tested included mouse breast, colon, and lung tumors, human tumor grafts of the same types, and an additional mouse leukemia and melanoma.

This approach identified new active agents that would have been missed by the mouse tumor models. However, many key disease events, such as metastasis, did not occur in the graft models raising concerns they might miss effective drugs and limiting their predictive utility. In the 1990s, an NCI investigator tested 12 known anticancer agents against 48 human cancer lines transplanted into mice and found that 30 of the tumors did not show a significant response (Plowman et al., 1997). Subsequent changes in screening (see below) improved relationships between models and actual clinical results, but correspondence between experimental and clinical data has never been complete (Johnson et al., 2001).

While these changes took the NCI screen from a compound-oriented approach to a tumor-specific approach, the high cost required a two stage system in which the mouse leukemia model was the prescreen. Moreover, the bias against selection of drugs specifically active in solid tumors remained a problem, and demonstration of significant preclinical activity in human breast, colon, or lung cancer graft models by a given drug did not necessarily predict for clinical activity in patients with those diseases (Khleif and Curt, 2000).

The 1980s and 1990s

By 1982, 2,164 compounds had been assigned to the tumor panel, of which 1,084 were tested against the complete panel. Although the NCI attempted to introduce more rational criteria into the selection of screening candidates, particularly novelty of structure and known biological activity, the majority of compounds tested continued to be random chemical entities submitted by chemical and drug companies and academic laboratories.

In the mid 1980s, NCI was questioning the value of the program given its slowing yield of promising drugs and failure to produce new solid tumor agents, but decided not to cancel out of concern that the private sector would not fill the void. New molecular screening targets, for example, growth-factor inhibitors, oncogene products, and protein kinases, were considered, but NCI decided to develop a cell-line-based screen representing the major classes of solid tumors because that would allow relatively inexpensive and rapid testing against broad panels of human tumors and would be adaptive to the needs of natural product screening (Chabner, 1990). The screen was designed so that for each compound tested, both the absolute and relative sensitivities of individual cell lines comprising the screen were sufficiently reproducible that a characteristic profile or fingerprint of cellular response was generated.

Since 1990, the program has used a primary *in vitro* screen followed by evaluation in hollow fiber (see discussion below) and tumor graft models (Sausville and Feigal, 1999). The decision to abandon large-scale *in vivo* screening disappointed many in the pharmaceutical industry (DTP Program Review Group Report, 1998). NCI maintained that the *in vitro* screen would provide a practical means for the selection of compounds of interest for *in vivo* testing, thereby reducing the randomness and cost of less discriminating screening methods and allowing universities (which lacked the resources to submit the larger quantities of agents needed for *in vivo* testing) to submit more compounds for initial testing (Grever et al, 1992).

The DTP Human Tumor Cell Line Screen

The infrastructure for a large-scale cell-line screen was built at NCI's Frederick Cancer Research and Development Center, initially equipped for 10,000 compounds and currently accommodating 20,000 compounds per year. The screen uses 60 human tumor cell lines, representing leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney. Natural products collected in an NCI repository are also a major source of chemical entities screened (see Box 1)

The aim of the screen is to prioritize the further evaluation of synthetic or natural compounds that demonstrate selective growth inhibition or cell killing of particular tumor cell lines. A 60 cell line dose response data set produced by a given compound results in a biological response pattern that can be utilized in pattern recognition algorithms to assign a putative mechanism of action to a test compound, or to determine that the response pattern is unique. Although the particular growth inhibitory response of a single cell line might be relatively uninformative, the pattern of response of the cell lines as a group can be used to rank a compound according to the likelihood of sharing common mechanisms. The COMPARE computer algorithm quantifies this pattern (Monks et al., 1997), and COMPARE searches the database of screened agents to compile a list of the compounds that are most similar (Paull et al., 1989).

Following characterization of various cellular molecular targets in the 60 cell lines, it may be possible to select compounds most likely to interact with a specific molecular target. Successes in use of the screen to identify the underlying mechanisms of the multi-drug-resistant form of cancer have led NCI to develop collaborations to go beyond growth inhibition and cell killing to characterizing mechanisms of action through the expression of molecular targets in the 60 cell lines (Monks et al., 1997). Examples include cancer suppressor gene status (Weinstein et al., 1997) or the presence of an oncogene (Koo et al., 1996).

Three Cell Line Prescreen

In early 1995, NCI, in reviewing screen data, observed that many agents were completely inactive under the conditions of the assay. A protocol for a three-cell line prescreen was developed in collaboration with the Information Technology Branch of DTP that could eliminate approximately 50 percent of drugs from 60 cell line testing

without a significant decrease in ability to identify active agents and thus increase the throughput and efficiency of the main cancer screen with limited loss of information.

Hollow Fiber Technology

In the mid 1990s, for agents identified by the COMPARE algorithm, NCI began incorporating assays using semi-permeable hollow-fibers implanted in animals in the *in vivo* phase of drug development. These fibers allow tumor cells to grow in contact with each other, and more than one tumor can then be implanted into a single animal providing greater efficiencies than would be obtained through a single *in vivo* experiment (Khleif and Curt, 2000). A standard panel of 12 tumor cell lines is used for the routine hollow fiber screening of compounds with *in vitro* activity, and alternate lines can be used for specialized testing on a non-routine basis. The premise of this technique is that advancing potential anticancer agents identified in an *in vitro* screen to preclinical development requires a demonstration of *in vivo* efficacy in one or more animal models (Hollingshead et al., 1995), and hollow fiber screens appear to correlate well with clinical results (Johnson et al., 2001).

A Critical Review of NCI's DTP

In 1997, the Director of NCI formed the Developmental Therapeutics Program Review Group (called the Horwitz Committee after its chair, Susan Horwitz of Albert Einstein College of Medicine) and charged it with the task of making recommendations to enhance NCI's ability to discover new and useful antitumor drugs, particularly those with unique and novel mechanisms of action rather than simply antiproliferative effects.

The Horwitz Committee was enthusiastic about enhancing DTP decisions concerning its resource allocations through an oversight group established to continuously monitor the discovery and development process for any drug target or drug candidate by bringing together and coordinating distinct proposals from different laboratories or institutions nationwide.

Box 1: The Natural Products Repository

Since 1986, DTP has acquired plants and marine organisms through collection contracts performed in over 25 tropical and subtropical countries worldwide. As of 1999, more than 50,000 plant samples have been collected, as well as 10,000 marine invertebrates and marine algae. In undertaking these collections, NCI has committed itself to the conservation of biological diversity, as well as to policies of fair and equitable collaboration and compensation in interacting with the source countries participating in the collection programs. Each organism is extracted in the Natural Products Extraction Laboratory and the extracts are stored in the Natural Products Repository. Both facilities are operated by a contractor at the Frederick Cancer Research and Development Center. NCI considers the Natural Products Repository as a national resource, and extracts from the Repository are available for distribution to qualified organizations. Access to these programs is subject to signing a Material Transfer Agreement protecting the rights of all parties.

The Committee recommended to DTP: a focused screening program for active compounds using assays for which it has developed expertise and capacity; providing public access to its repository of compounds, research tools, and information databases; working with the government, academic, and industrial communities to develop, evaluate, and deploy new assays in both the internal and external scientific communities; and fostering a more collaborative approach to screening by serving as a matchmaker between chemists and biologists for the analysis of novel agents. Along these lines, the Committee recommended that DTP assume a leadership position in informatics, facilitate developing cancer therapeutics through expansion of its current operations, and increase access of extramural investigators to natural product repositories, select chemical libraries, engineered cell lines, chip and microarray technology, standardized reagents for cancer immunotherapy, and information databases. It further recommended that extramural funding be directed to support cooperative groups in different parts of the country and facilitate alliances between government, academic, and industrial resources (http://deainfo.nci.nih.gov/advisory/bsa/bsa_program/bscdevtherprgmin.htm).

Recent Changes in the Drug Development Algorithm

As a result of the Horwitz Committee's recommendations, the algorithm for the drug discovery pathway was changed. The committee recommended that the 60 cell line screen be preceded by a 3 cell line screen to first identify lead antiproliferative agents. A subset of compounds identified in this manner could then be analyzed in the 60 cell line screen to gain insight into a compound's mechanisms of action. The next step would be to define the mechanism of action or identify a novel compound as affecting a defined biochemical, cell, or tissue physiological endpoint with the intent of advancing to development only after an effort to establish a molecular endpoint of a compound's action. Further characterization of a compound could then be conducted in an appropriate animal model or via the hollow fiber assay.

The new algorithm relies less on activity in tumor graft models and more on a priori definition of a mechanism of action or molecular target in defining a strategy for subsequent development (Sausville and Feigal, 1999). In essence, an effect on an important molecular target becomes a constant signal after which pharmacologic, scheduling, and toxicologic studies follow. This would also allow incorporation of target or molecular endpoints in early clinical trials to follow logically from the preclinical experience. More formal safety testing would be undertaken for suitable compounds, proceeding to phase I clinical trials using the biological, pharmacological, and toxicological properties to define optimal dose and schedule conditions for human studies.

NCI is also reclassifying the cells in the panel according to the types of genetic defects the cells carry. That way, if drugs that address the specific defects or targets can be identified, they could theoretically be matched to a patient's tumor cell makeup. DISCOVERY is a computer program that uses a clustering algorithm to group

compounds by cellular response patterns. The data collected from the primary *in vitro* screen is analyzed with the help of algorithms and assembled into unique patterns of activity that cut across cell types. Correlations of compound activity are made with mechanisms of action for particular molecular targets and then used to generate hypotheses that relate to the potential targets, and the molecular targets of unknown drugs can be deciphered by analyzing their cell line screen data and comparing it with the activity of the agents in the database. These analyses and correlations have recently been enhanced through the use of publicly available data on gene expression patterns for thousands of expressed genes from NCI's collaboration with Brown and Botstein (Ross et al., 2000) as a means of aligning response patterns with patterns of gene expression (Sausville and Johnson, 2000).

DTP's Efforts in Biological Response Modifiers

The Biological Resources Branch (BRB) is one of the extramural arms of DTP. The program supports preclinical and early clinical studies of biological response modifiers (BRMs) through a program of grants and contracts. These studies assess the effects of novel biological agents and explore relationships of biological responses with antitumor activity. An NCI Preclinical Repository distributes selected agents for peer-reviewed intra- and extramural preclinical studies. Other contracts support the production and *in vivo* evaluation of monoclonal antibodies, immunoconjugates and other biologicals.[1]

BRB staff also provide oversight of the Biopharmaceutical Development Program (BDP) at the Frederick Cancer Research and Development Center, which produces a variety of biopharmaceuticals under current Good Manufacturing Practices (cGMP) for Phase I and II human clinical trials or advanced preclinical animal testing. NIH grant holders and other peer-reviewed scientists are encouraged to contact the BRB for discussions at an early stage regarding use of this resource. NCI program funding can also be provided through the Rapid Access to Intervention Development Program (RAID) mechanism (see further discussion below) or through DTP.

There are three types of production services: small quantities of interesting new proteins that may be implicated in disease processes and would also support testing in small animal models; larger quantities of well-characterized material for preclinical testing to support evaluations of efficacy and toxicity in appropriate animal models of disease; and clinical-grade material to support final preclinical work, IND submission, and Phase I and II clinical trials.

The development group deals with incoming projects at initial stages including evaluation, yield, efficiency, and characterization of products. This group also focuses on process development after initial evaluation for supporting cGMP production in BDP. The laboratory has the capacity to construct recombinant bacterial strains and cell lines, has expertise in a variety of fermentation processes including bacterial, yeast, fungal,

[1] http://web.ncifcrf.gov/research/brb/mission.html

insect, and mammalian cell culture, and focuses on process optimization[2] with implementation of highly efficient bioreactor production utilizing mammalian and microbial fermentation pilot plants with the capacity for product recovery.

The Advent of Molecular Targeting

Recent advances in molecular biology have dramatically improved understanding of how cancer cells work. Specific molecules have been identified that are responsible for the initiation and progression of tumors. This provides the opportunity to move beyond empiric screening of agents by their effects on tumor cell growth to detection targeted to a particular molecule of biologic importance in cancer development or progression. In the late 1990s, NCI's efforts to revamp its preclinical drug discovery work were refocused in this direction (Sausville and Feigal, 1999). The tools for this approach include sequence information that defines the primary structure of relevant target molecules; expression vectors for large scale target production; physical and computational techniques to allow routine elucidation of three-dimensional structure; advances in screening technology to promote increased efficiency in assessing large numbers of candidate lead structures; and synthesis approaches to generate large numbers of test compounds (Sausville and Feigal, 1999).

Currently, methods for target identification are relatively slow and unreliable. The NCI multiple cell line screen, when employed in conjunction with cell-based assays, provides a useful empirical method for identifying molecules that are likely to target DNA or proteins or may be novel. But for small molecules with novel activities, this screen cannot suggest a likely target (Horwitz Committee, 1998). Researchers have tended to rely on methods in which the small molecule is used to purify its target from a cell extract, usually by affinity chromatography, although this method tends to be tedious. Through investments in genomics and related technologies, a more radical approach to target identification is now becoming available using new tools (called hybridization technology) that allow the study of effects on a whole genome, not just an isolated portion.

In 2000, as a first step to refocus its efforts in this area, NCI announced the availability of Molecular Target Drug Discovery grants. Program announcements for this initiative stated that "Rather than depending on *in vitro* and *in vivo* screens for antiproliferative activity, investigators can now focus on new molecular targets and pathways essential for the development and maintenance of the cancer phenotype."[3] The NCI announced that it was reorganizing its drug development programs from early drug discovery to the conduct of clinical trials in order to bring forward new types of agents based on strong rationales. Clinical evaluation of new agents would include appropriate measurements to verify target modulation. Investigators funded through the program were asked to identify a novel molecular target, to validate the target as a basis for cancer drug discovery, and to develop an assay for the target. Molecular target laboratories are

[2] http://web.ncifcrf.gov/research/brb/BDP/index.html
[3] http://grants1.nih.gov/grants/guide/rfa-files/RFA-CA-00-002.html

funded to produce libraries of potential anticancer compounds for distribution, to develop screening assays, and to confirm a drug's initial ability to alter its target.

As of 2004, 76 research groups were being supported via this initiative -- investigating an aberrant protein that enables cancer cells to evade programmed cell death, a "stress response" protein that is overexpressed in tumors and may play an important role in cancer growth, or how DNA changes (methylation) can lead to cancer.[4]

The Cancer Genome Anatomy Project

The Cancer Genome Anatomy Project (CGAP) is an interdisciplinary program established and administered by NCI to achieve a comprehensive genetic description of normal, precancerous, and malignant cells so as to determine the changes that occur when a normal cell is transformed into a cancer cell, and then to apply that knowledge to the prevention, detection, and management of cancer.[5]

Since its inception in 1996, the program has had four primary initiatives. The Human Tumor Gene Index identifies genes expressed during the development of human tumors. The Cancer Chromosome Aberration Project characterizes the chromosomal alterations that are associated with malignant transformation. The Genetic Annotation Index identifies and characterizes the different genetic DNA sequences associated with cancer, and the Mouse Tumor Gene Index identifies genes expressed during the development of mouse tumors.

CGAP supports the production of serial analysis of gene expression (SAGE) libraries and their sequencing, while the National Center for Biotechnology Information (NCBI) has created a repository for the sequence data, has developed data processing algorithms, and has developed and maintained the SAGEmap website at NCBI.[6] Everything is shared openly with the research community. The CGAP web page contains databases of a wide array of human and mouse genomic data and provides information on new experimental methods. Biological reagents developed through the program are available to researchers at cost. In the future, the program may move into the development of functional genomics and proteomics databases.

According to NCI, researchers have started mining the CGAP databases and are already discovering new, potentially cancer-causing genes, identifying candidates for molecular targeting research, and helping to build assays for cancer cell signature research. Investigators who are funded through the program are required to agree not to patent the sequences they acquire. And because NCI has obtained a declaration of exceptional circumstances under the Bayh-Dole act, sequencing project contractors do

[4] http://plan.cancer.gov/scipri/targets.htm#identifying
[5] http://cgap.nci.nih.gov/
[6] Established in 1988 as a national resource for molecular biology information, NCBI creates public databases, conducts research in computational biology, develops software tools for analyzing genome data, and disseminates biomedical information to facilitate better understanding of molecular processes affecting human health and disease.

not retain title to inventions developed with the federal funds, and NCI can require immediate disclosure of all such data.

Other NCI Drug Development Activities in Molecular Targeting

The Laboratory of Molecular Technology (LMT)[7] in Frederick, Maryland, is an integrated molecular biology laboratory focusing on high-throughput gene discovery and analysis including advanced sequencing, genetics, genomics, and proteomics technologies, together with associated bioinformatics and information management. General access to these advanced technologies is provided to the NCI community through the LMT core service laboratories.

The lack of adequate animal models has led to the development of transgenic mouse models to be used as preclinical assays to determine the likelihood of success for novel agents being considered for clinical studies. The Mouse Models of Human Cancers Consortium[8] involves 20 groups of academic researchers who have created and are making available to researchers mice with defined genetic alterations that predispose the animals to certain types of cancer that could serve as a basis for testing new molecular targeting treatment and prevention strategies. Academic members of the consortium are developing ties to pharmaceutical industry sponsors to facilitate the testing and evaluation of new compounds in these mouse strains.

The high cost of X-ray and nuclear magnetic resonance equipment and the specialized expertise required to run experiments on these instruments exclude large numbers of scientists who are interested in pursuing molecular structural studies using these technologies. Many of the most interesting structural problems will involve complex systems, such as those involved in multistep intracellular processes. Multicomponent complexes are difficult to crystallize, and, frequently, usable structural data can be obtained only by using a scarce (synchrotron beam) technology. NCI is collaborating with the National Institute for General Medical Sciences on the National Beam Program to provide both this technology to quickly identify the structure of important molecular targets in cancer cells and efficient computer modeling to identify potential anti-cancer agents suited to hit the targets based on these structures.

Several NCI initiatives are aimed at creating libraries of synthetic, biological, and natural compounds for testing against validated molecular targets. Samples of these are provided at no cost to investigators. NCI has made available more than 140,000 synthetic chemicals, 80,000 natural products extracted from plants and marine organisms, and a variety of biological agents for use in studying the compounds.

Specific assays are used to identify those that hit defined target molecules. Approaches used to achieve these goals include: the National Cooperative Drug Discovery Group Program (NCDDG), funded as cooperative agreements in response to a Request for Applications (RFA)[9] that was established in 1983 and supports 13 multi-

[7] http://web.ncifcrf.gov/rtp/labs/LMT/
[8] http://emice.nci.nih.gov/emice/
[9] http://dtp.nci.nih.gov/branches/gcob/gcob_web3.html

disciplinary groups involved in the discovery of new, synthetic or natural-source derived anticancer drugs; and the Biology-Chemistry Centers, funded as program project grants[10] that support six multi-disciplinary research centers that bring together approaches to the generation of structural diversity and novel, specific assays directed at molecular events or targets important in the cancer process and thus suitable for cancer drug discovery.

Outstanding Needs in Preclinical Cancer Models

A number of preclinical mouse tumor models have been developed. Unfortunately, no one model serves as a satisfactory predictor of human cancer, but the experience gained over the past three decades by using these models for studying the effects of various experimental therapeutics can serve as a baseline for assessing new targeted agents. Four major types of *in vivo* models are available to assess the efficacy of potential new therapeutics in cancer. Each model, as described below, has advantages and disadvantages.

A variety of native tumor types in immunocompetent mice and rats exist, and these models are reliable, available in numbers adequate for good statistics, low cost, and with well established responses to current anticancer therapies. The disadvantages are that the systems are fully rodent and that these fast growing tumors may not accurately model human tumors.

Genetically engineered mice that will develop tumors are generally immunocompetent, and the tumors are genetically mouse and localized in the usual sites. The disadvantages of these models are the requirements for breeding (and frequently, licensing) the animals that make these models high cost. The tumors usually develop late in the animal's lifespan, so these models are slow in developing. Moreover, there are few tumor types available, and it is difficult to obtain enough animals to establish reliable statistics. Importantly, very few of these models have been validated as representative of human disease through molecular markers and response to current anticancer therapies.

Human tumor grafts in mice have the advantage of human malignant cells of a wide variety of types and, in many cases, reliable tumor growth. The response of many of these tumor models to current anticancer therapies is well-established. The disadvantages are that the hosts are immunodeficient, the tumors are generally slow-growing, the tissue supporting the cancer cells is of mouse origin, and the animals are costly and require special housing. Due to the cost of the studies, fewer animals may be used than are actually needed for reliable statistical analysis. Unfortunately, all animal models suffer from inconsistency in predicting responses of human cancers to therapy.

There are other models that are used in studying chemoprevention and metastasis. Carcinogen-induced tumor models have been used in chemoprevention research but have been difficult to apply to therapeutic research. Models of metastatic disease use rats or mice that have naturally metastatic cancers, or involve injecting tumor cells intravenously to produce lung metastases, intrasplenically for liver metastases, intracardially or

[10] http://dtp.nci.nih.gov/branches/gcob/gcob_web18.html

intratibially for bone metastases, or into the internal carotid artery for brain metastases. A number of experimental cancers have now been developed that produce fluorescent markers that, with the necessary instrumentation, allow detection of metastases by fluorescence. These genetically engineered models are costly, and natural or engineered models have highlighted the problem that tumor response to therapy markedly depends upon the anatomical location of the disease.

The lack of uniform standards for determination of tumor volume doubling time, tumor growth delay, $\log_{10}$ cell-kill, or other endpoints is a weakness in the field. Experiments are frequently terminated before any endpoint is reached. Guidelines for the conduct and analysis of *in vivo* studies of new therapies, based on results from previous testing, could help developers weed out less active compounds earlier in the process. Guidelines to establish uniform criteria for antitumor activity and for *in vivo* data analysis would allow comparisons to be made before new therapies are taken to clinical trial. For targeted therapies, tumor expression of the target should be confirmed. Activity in several tumor models establishes a stronger case for a new agent than activity in a single model. Use of established methods for the determination of additivity/synergy for combination regimens should be the standard. An agent that survives higher hurdles during preclinical testing would presumably have a greater chance of clinical success, and guidelines for uniform data gathering and data analysis should allow improved selection of agents for clinical trials.

Toxicologic Evaluation at NCI

Once a compound of interest is identified, animal models are critical to assess preclinical toxicology. In the 1970s, NCI used only dogs and monkeys in its preclinical toxicology protocols (Khleif and Curt, 2000). In 1979, NCI and the FDA reviewed existing data and concluded that toxicity studies performed in mice could in most cases replace the more costly and time-consuming large animal studies. Some believe that the NCI toxicology protocol has performed well in predicting safe initial doses for clinical trials (Khleif and Curt, 2000). Others believe that it is costly and non-productive to generate large amounts of animal toxicology data without some guidelines or assessment of whether the data are of any use (Schein, 2001). Clearly, when it comes to qualitative or organ-specific forms of toxicity, the role of preclinical toxicology studies in animal models has been ambiguous.

The development of drugs within NCI has evolved into two stages at present, each of which requires a toxicologic evaluation. The first involves a preliminary assessment of toxicity (range-finding studies) usually in two preclinical animal models (rodent and nonrodent) with the determination of maximum tolerated dose and drug behavior in the animal (pharmacokinetics) in both species. If the drug meets the program criteria for full-scale development, a more complete toxicity evaluation (IND- directed studies using the proposed clinical route and schedule) is performed that leads to the filing of an IND (Tomaszewski and Smith, 1997). FDA has defined the battery of preclinical studies that are considered important for assessing the safety of oncology drugs prior to filing an IND. In the past decade, NCI has conducted agent-directed drug development projects, including toxicologic evaluations on eight drugs and concluded that their evaluations

allowed an impressive prediction of maximum tolerated doses and dose-limiting toxicities.

NCI's Role in Facilitating Clinical Translation

Early drug development work is more typical of traditional academic research, and downstream preclinical and clinical testing has traditionally been the domain of industry. While it is often the case that a company will partner with, or acquire, promising research at the transitional stage, academic researchers often wish to carry forward research that originated in their institutions. To aid them, NCI has initiated several programs aimed at reducing or removing the rate-limiting barriers that typically delay clinical validation, for example, scale-up of production, development of suitable drug formulations, development of analytic methods, stability testing, animal toxicology, and planning for clinical trials (Schein, 2001) -- processing challenges that are routinely undertaken by industry.

The NCI RAND and RAID Programs

NCI's Rapid Access to NCI Discovery Resources (RAND) program was initiated to make available to academic institutions on a competitive basis the discovery and early preclinical development contract resources of DTP so as to provide a broad range of early preclinical assistance for anticancer therapeutic discoveries in academic laboratories. The program is intended to remove the most common barriers between basic research and the development of new molecular entity therapeutics. It assists academic investigators in the discovery of small molecules, biologics, or natural products through mechanisms such as the development of high-throughput screening assays, computer modeling, recombinant target protein production and characterization, and chemical library generation. It also assists in the development of analytical methods for pharmacokinetic and metabolic studies, and *in vivo* pharmacokinetic, toxicity, and efficacy studies. Compound samples accepted after DTP review can be screened for the academic originator using the NCI's three cell line, one day prescreen, and a follow-up of actives in the NCI 60 cell line screen.

All output from a RAND project is returned to the originator of the project as synthesized or isolated materials, high-throughput screening or pharmacokinetic methods, informatics output, or *in vivo* screening results, among others. NCI will not acquire intellectual property rights to inventions made by its employees with research materials under RAND (or the RAID program, described next), unless the originating investigator and NCI mutually agree that it is in the investigator's best interest. If an NCI contractor is in a position to file an invention report and elects to retain rights under the Bayh-Dole Act, the contractor will, as provided under the contract, offer the principal investigator a first option to negotiate a license to the invention.

Once the optimal compound is selected, the Rapid Access to Intervention Development (RAID) program facilitates further preclinical development and generation of evidence that a new molecule or approach is a viable candidate for expanded clinical evaluation. RAID provides academic or non-profit institutions NCI resources for the pre-

clinical development of drugs and biologics on a competitive basis. Resources include chemical synthesis and good manufacturing practices, formulation research, clinical dose form manufacturing, bulk manufacture of monoclonal antibodies, and formulation for production of recombinant proteins, among others.

RAID is intended to remove the most common barriers between laboratory discoveries of new molecular entities and clinical trials. The program, in December 2004, provided resources to academic institutions in 52 projects [11] , but it is not intended to be a pipeline for materials for NCI-held INDs. Most of the products in the RAID program will be studied clinically under investigator-held INDs at the originating (or a collaborating) institution. RAID resources are limited, and it is not an unconditional commitment to develop a particular compound for the clinic, nor is it meant to assist industry in the absence of an academic partner.

RAID is also not a grant program to a particular laboratory. It is expected that the great majority of resources committed through RAID will be through use of NCI new-agent development contracts and of NCI staff expertise in service of meritorious academic projects. Some steps in the process may best be carried out in the originating laboratory, in which case NCI will initially attempt to provide necessary support through existing suitable funding vehicles, but this pathway for support may not be the ultimate avenue used.

RAID is designed to accomplish the tasks that are rate-limiting in bringing discoveries from the laboratory to the clinic. Division of Cancer Treatment and Diagnosis contractors perform the work in direct consultation with the originating laboratory. In some cases, RAID supports only the one or two key missing steps necessary to bring a compound to the clinic; in other cases it supplies the entire portfolio of development tasks needed for an IND.

NCI-Industry Interactions

NCI has pursued several mechanisms to partner with the private sector in drug development. These mechanisms are in addition to the typical industrial relationships allowed by law and NIH policy, for example, Cooperative Research and Development Agreements (created by the Federal Technology Transfer Act of 1986 to enable cooperative research and development relationships and technology transfer between NCI or other federal agencies and industry) and Small Business Innovation Research grants (authorized in the Small Business Innovation Act of 1982 which, through a set aside of agency resources, provides grants for up to two and a half years to support research and development leading to commercialization in small-business-qualified companies.

The Drug Development Group provides support for academic and corporate-derived compounds when NCI is responsible for conducting and monitoring the drug's clinical development. A number of promising agents have been developed through this program. A novel compound (PS 341) presented to NCI by Millennium Pharmaceuticals, was the

[11] http://plan.cancer.gov/scipri/targets.htm

first in a new class of agents that take aim at a new cellular target, the proteasome enzymes. These enzymes play an important role in the breakdown of proteins that regulate the cell cycle, and inhibition of the breakdown of these proteins by the new agent can lead to cancer cell suicide. Histone deacetylase (HCAC) was another agent pursued through this program. Certain cancer-causing genes induce cancer when they block the normal expression of healthy genes. HCAC inhibitors relieve this suppression. In cooperation with extramural organizations, NCI has studied the anti-tumor effects of several such inhibitors, including pyroxamide, an inhibitor identified by an NCI-supported cancer center that considerably reduced tumor growth in animals.

The Flexible System to Advance Innovative Research (FLAIR) provides funds to small businesses to develop cancer therapeutic and prevention agents from basic discovery to clinical trials. As of December 2004, 20 active FLAIR grants and phase I clinical trials were supported by the FLAIR program.

The Radiation Modifier Evaluation Module (RAMEM) program serves individual investigators and industry in the design and development of treatment programs for the use of novel molecular, biologic, and cytotoxic agents in conjunction with radiation therapy. Integration of molecular imaging, molecular signatures, and molecular therapeutics with radiation therapy is a high priority of NCI's Intramural Program because new anti-cancer agents may ultimately be used in combination with radiation therapy.

Preclinical and clinical research with novel agents for cancer treatment and prevention requires usable tools to determine that the intended molecular target producing or associated with cancer has been affected by the agent. The Interdisciplinary Research Teams for Molecular Target Assessment is a new program that enables interdisciplinary teams of scientists to develop such tools. The teams will define the molecular basis for these research tools and develop and validate novel biochemical, pathological, pharmacologic, immunologic, molecular, or imaging methods and reagents to measure the effect of new target-directed drugs in proof-of-principle laboratory models and clinical trials. These methods and reagents must, therefore, be suitable for *in vivo* use in animal models and in human beings. The first set of applications for this program was funded in early FY 2001.[12]

Sponsorship of Clinical Trials by NCI

In 1955, the National Cancer Institute began to organize clinical trials of the first effective anticancer agents in leukemia patients. Since then, NCI has become the largest U.S. network for clinical trials of any type, with support through a variety of mechanisms, including the largest, the Cooperative Group Program and the Cancer Centers Program, as well as grants and contracts to individual investigators and institutions. NCI-supported trials are carried out in diverse settings, including cancer centers, academic medical centers and community hospitals. Early trials (phase I and

[12] RFA: CA-00-001, November 10, 1999.

Table 1: NCI-Sponsored Clinical Trials (March 2004)	
All Trials	
Phase I	361
Phase II	707
Phase III	203
Phase IV	0
Treatment	1072
Phase I	351
Phase II	658
Phase III	156
Phase IV	0
Screening	13
Prevention	50
Supportive Care	118
Diagnostic	45
Genetic	25
ALL NCI-Sponsored	1260

SOURCE: NCI Web site, March 24, 2004

many phase II) are often carried out by single investigators or small groups at of a few institutions. Phase III trials are generally associated with the Cooperative Groups.

As of March 2004, NCI was sponsoring about 1200 clinical trials. About 1000 are treatment trials, and the rest are supportive care, screening, prevention, diagnostic and genetic. Most are phase I and II trials and about 200 are large, phase III trials, the mainstay of the Cooperative Groups (Table 1).

The Cooperative Group Program

As noted earlier, the Clinical Trials Cooperative Group Program was established by NCI with a congressional appropriation for this purpose in the 1950s when most new anticancer agents were being developed through NCI funding. Over time, through consolidations and other changes the Program reached its current status of 12 NCI-supported Cooperative Groups, made up of academic institutions from the United States, Canada (National Cancer Institute of Canada, Clinical Trials Group), and Europe (European Organization for Research and Treatment of Cancer), emphasizing phase III studies, 11 for adult and the 12th, the Children's Oncology Group, for childhood cancer. Some groups (Children's Oncology Group) consist of investigators with a particular specialty, others (Radiation Therapy Oncology Group) study a specific therapy, and still others (Gynecologic Oncology Group) focus on a group of related cancers. The 2004 Cooperative Clinical Research budget of $180 million supported the accrual of about 28,000 patients that were contributed from more than 1,700 institutions to group

coordinated trials at about 1000 sites, although 85 percent of patients are enrolled at about one-quarter of the sites, mainly large cancer centers. The Program is explicitly designed to promote and support clinical trials of new cancer treatments, explore methods of cancer prevention and early detection, and study quality of life and rehabilitation issues during and after treatment (Schilsky, 2002).

Cooperative Group investigators may work on non-Cooperative Group trials, such as early phase and phase III NCI or industry trials at their institutions or phase III trials cosponsored by industry and carried out by Cooperative Groups. The latter trials using investigational agents proprietary to a pharmaceutical or biotechnology company are subject to specific cooperative research and development or clinical trials agreements (CRADA or CTA)[13] dealing with intellectual property, confidentiality, and other uses of the investigational agent (http://ctep.cancer.gov/industry/industry.html). All the cooperative groups are subject to on-site monitoring under NCI guidelines.

The Cooperative Groups and the NCI-designated cancer centers collectively conduct a larger number of trials and enroll more patients than other entities, but other groups now compete in this territory. For example, U.S. Oncology, a for-profit network of cancer providers that treats about 16 percent of U.S. cancer patients, has accrued over 16,000 cancer patients into clinical trials and played a significant role in FDA approval of eleven anticancer drugs that have entered the market over the last ten years (http://www.usoncology.com/OurServices/USONResearch.asp), and there are other entities for organizing trials, such as the clinical trials network of the National Comprehensive Cancer Network (NCCN), as well as private sector contract research organizations Some of these groups extend the reach of clinical trials to patients who would otherwise be outside the membership of the Cooperative Groups, others may draw from the same pool of patients, for example, NCCN members are 19 large U.S. cancer centers that are also part of the Cooperative Group system.

As productive as the Cooperative Groups have been, the conduct of phase III trials has been seen as problematic for many years. A major issue has been, first of all, the slow and difficult procedure for developing, reviewing, and initiating protocols. Secondly, patient accrual can continue over many years before the goals are met. As a result, by the time trials are completed, the questions being addressed may no longer be relevant. Furthermore, the 28,000 patients entered into Cooperative Group trials annually comprise only about 2 percent of the 1.3 million adults diagnosed with cancer each year (ACS, 2002), or about 2 percent of the new cases and a much smaller percentage of all people living with cancer.

Finally, while phase III trials are, with rare exceptions, required for final FDA new drug approval, most of the trials that in practice define the uses of a cancer drug take place after FDA approval, the importance and scope of such trials in cancer being far greater than for drugs for other conditions. A whole range of tumor types other than those for which the drug is approved, and in combinations with a wide variety of other

[13] CRADAs for cancer and other therapeutics may generate controversy because of perceived excessive company profits or pricing. For example, the NCI-Bristol Myers Squibb CRADA for paclitaxel created a multibillion dollar drug for the company (Chabner and Roberts, 2005)

drugs, are very often studied once a drug becomes available, and the Cooperative Groups play a leading role in this work. This complicates the federal role in developing and regulating cancer therapies.

Changing to Meet the Coming Needs

If, as is anticipated, the number of new cancer drugs in development increases—possibly dramatically—the NCI clinical trial network will be pressed to meet new challenges, including: greater involvement with pre-approval trials; more rapid development of protocols for post-approval trials; improving accrual rates; greater numbers of clinical questions likely to be generated by the larger numbers of agents (many of which should have known molecular targets); among others

In addition to increasing enrollment in trials, efforts to select patients based on matching cancer molecular profiles with drug targets might identify the most appropriate patients for trials of particular agents. Industry is clearly moving in this direction, and NCI has the tools to contribute to the process, and could facilitate collaborations in this area (Canetta, R., personal communication to the National Cancer Policy Board, 10/11/01). A similar concept may move phase I dose-finding trials from the goal of the maximum tolerated dose to a focus on a biologically effective dose, that is, matching the dose of a targeted agent to levels of the target measured in blood and/or tumor tissue. Monitoring the activity of new agents in this more precise way could provide an anticancer effect through saturation of activity against the tumor molecular target before general clinical toxicity appears in the patient, but will require tests of appropriate markers in tumor and blood specimens from each patient studied in phase I trials.

Facilitating drug development needs of this sort could be accomplished by good use of existing (some relatively new) programs. The NCI's Early Detection Research Network (EDRN) already funds molecular marker laboratories at various institutions around the country. These laboratories are focused on discovery of markers for cancer diagnosis, but they are also aware of the value of many of the markers as targets for cancer therapy or prevention. Such markers can be picked up by industry, developed in collaboration with industry, or used in trials by any of the entities described earlier. Core laboratories funded by NCI's Specialized Program of Research Excellence (SPORE) could serve the same function. As described in the Critical Path section of Chapter 3 of this background paper, FDA is also focusing on the development of markers and their use in improving evaluation of new medical products (drugs, biologics, and devices) in the recently announced Critical Path Initiative and Critical Path Opportunities List (http://www.connectlive.com/events/fdacriticalpath/ - 12/3/04)

Potential administrative difficulties stem from the fact that that the EDRN is overseen by the Division of Cancer Prevention, the Centers and SPOREs by the Office of the Director and the Division of Cancer Biology, Diagnosis, and Centers, and the cooperative groups by the Division of Cancer Treatment and Diagnosis, and each office and division has its own priorities and responsibilities. However, reasonable communication, coordination, and the normal process of publication and dissemination of scientific advances should help to make these resources available in drug development,

and NCI is aware of these coordination, academic-industry relationship, managerial, and other challenges (Klausner, R., personal communication to the National Cancer Policy Board, 4/10/01).

Recent Changes in the Cooperative Group Program

In 1996, in response to growing concerns that its clinical trials portfolio was increasingly inefficient and unresponsive to changing needs—including the Cooperative Groups Program as a centerpiece of its clinical trials efforts—NCI commissioned an external review of its clinical trials program in its entirety (DTP Program Review Report, 1997). In the resulting document, called the Armitage Report after its chair, James Armitage, the Review Group wrote that the clinical trials system is "an intricate and large research laboratory without walls. This complexity has bred inefficiencies and eroded the ability of the system to generate new ideas to reduce the cancer burden." The Review Group considered recruiting and retention of clinical scientists, recruiting of participants to clinical trials, improving clinical trials methodology, increasing collaboration and cooperation in clinical trials, and NCI's organizational framework and structure for implementation of clinical trials.

The Group recommended that NCI should: increase funding for cooperative groups to fully recommended levels; reduce and limit data collection to study endpoints and patient safety and fund some large simple trials in common cancers to establish treatment differences; enforce uniformity of data collection; enlist advocates, industry, and the FDA to develop uniform standards and reporting requirements; provide cooperative groups and cancer centers with the means to access all relevant electronic databases and test the new NCI informatics system; and develop strategies to convince payers that clinical trials represent a better standard of care and ultimately result in decreased costs.

As a result of this review, NCI created an internal implementation committee that developed constructive responses to these recommendations, among others. Several of these initiatives are highlighted or outlined more specifically in NCI's FY 2005 Bypass Budget (NCI, Nation's Investment in Cancer Research, 2004). For example, continued support of the Cancer Trials Support Network centralizes the common administrative, financial, and data collection activities of the cooperative groups. Since 2002, physicians outside NCI cooperative groups have been enabled to enroll patients into NCI-sponsored clinical trials. In 2003, NCI and FDA signed a multi-part Interagency Agreement to share knowledge and resources in order to enhance the efficiency of clinical research and the scientific evaluation of new cancer medications (see FDA chapter below). Other new initiatives strengthen the scientific planning for large trials and aim to double the rate at which Phase III trials are completed.

A persistent concern has been how well cooperative group efforts are coordinated, if at all, with clinical trials underway at NCI-designated cancer centers (P30) and SPORE (P50) programs. In 2003, a National Cancer Advisory Board (NCAB) review of the P30 and P50 programs recommended more coordination and standardization among these

entities and the cooperative groups.[14] The review group recommended that NCI develop a plan for improved coordination of all clinical research mechanisms, including cooperative groups, phase I and II contracts, SPOREs, and cancer centers, and convert the funding mechanism for cooperative groups and Phase I and II studies from a contract to an assistance mechanism. As of 2004, no action had been taken in response to the recommendations. However, in January 2004, the NCI announced the formation of a clinical trials working group to advise the Director and NCAB on the "development, conduct, infrastructure, and support necessary for the optimal coordination and future progress of the entire range of intramural and extramural clinical research trials" (The Cancer Letter, p.4, 1/9/04). In early 2005, this working group announced recommendations addressing better coordination, standardization of research tools, forms, contracts, and databases, and essential data collection, speeding of patient accrual, NCI certification of clinical oncologists, expansion of community-based regional IRBs, reduction of regulatory burdens, joint participation of FDA and NCI in meetings with industry, and establishment of a database on federally funded trials and of an external Investigational Drug Working Group, among others (The Cancer Letter, p. 1, 2/25/05). Steps to implement some of these recommendations will await future NCI action.

Review of Trial Topics

The Cooperative Group Program and the clinical trials programs more broadly continue to be scrutinized within and outside of NCI. These reviews have focused most closely on structural, administrative, and resource issues, and on the difficulty in accruing patients. They have not, by and large, examined the specific clinical questions addressed in the trials themselves to determine whether the best use is being made of this resource, although the most recent review suggested prioritization of trials so this may change. The possibility that large numbers of irrelevant trials are being carried out is remote, given the mechanisms in place to assure that each major trial is reviewed for clinical importance and soundness. However, the predicted change in the numbers and types of new cancer drugs emerging from the R&D pipeline suggests that a review of the types and mix of questions being addressed, particularly in phase III trials, could be useful.

Summary of the NCI Role

In 1955, Congress recognized the need for public investment in the discovery and development of anticancer agents. Since then, NCI has established a Developmental Therapeutics Program to support the programs necessary to its pivotal role in the worldwide effort to develop new agents to treat cancer. The DTP supports the preclinical development of novel therapeutic modalities for cancer, the acquisition, synthesis, and definition of activity in both *in vitro* and *in vivo* models of cancer, and the advancement of active agents in preclinical models toward clinical evaluation.

In recent years, the advent of genomics, combinatorial chemistry, and high-throughput screening for the identification of potential lead compounds has markedly expanded the number of candidate drugs in the pipeline (although, so far, not the number

[14] http://deainfo.nci.nih.gov/ADVISORY/ncab/p30-p50/P30-P50final12feb03.pdf

of effective drugs emerging). Progress in identifying the genetic and molecular bases for cancer has also intensified efforts to identify more selective and efficacious anticancer compounds. This predicted increase in the number of candidate drugs has already begun to alter the preclinical models and methods used in many therapeutic areas. The changes needed in clinical trials, however, have not kept pace.

A clear role for NCI, in collaboration with other NIH institutes and the outside scientific community, is in continuing to support large-scale science projects, as it has with the Human Genome Project and several current projects, such as, the Cancer Genome Anatomy Project and the Early Detection Research Network, among others. NCI has been very successful in carrying out, and assisting in, the process of developing new drugs for cancer. The challenge for the Institute is to continually reassess where its advantages lie, to consider its historical involvements in all phases of cancer drug development – to focus on basic science and discovery of interesting molecules against novel targets, or on preclinical and clinical development of academic or industry agents in coordination with the FDA in deployment, or both -- and to create opportunities for moving forward. As of late 2004, NCI was considering a review to carry out just such a reassessment (Doroshow, J., personal communication to the National Cancer Policy Board, 2004).

3

THE FOOD AND DRUG ADMINISTRATION

Introduction

This chapter of this background paper describes the Food and Drug Administration's (FDA) statutory authority and responsibility for new therapeutics, FDA programs begun as a result of legislative mandates or through the initiative of the agency itself, and interactions with sponsors and other entities, in particular, the National Cancer Institute (NCI). Not discussed (and the subject of a separate ongoing Institute of Medicine study) is post-marketing surveillance of drugs after development and FDA approval.

The FDA implements the laws passed by Congress relating to the approval and regulation of drugs and biological products in the United States; regulating clinical research on new drugs and biologics through the investigational new drug (IND) procedures; approving the marketing of new products for specific indications once safety and efficacy have been demonstrated in a New Drug Application (NDA; or a Biologics License Application (BLA) for biologics); and monitoring the safety of products following approval. In addition, the FDA regulates medical devices, veterinary drugs, food and food additives, and cosmetics and has special programs to encourage drug development for rare diseases and for children and procedures to allow patients with life-threatening diseases access to unapproved drugs.

Although few of the statutory provisions carried out by the FDA relate specifically to cancer, dedicated groups within FDA have been assigned to specific disease areas, including cancer; cancer-specific advisory bodies and guidance documents have helped to customize and standardize procedures for cancer drugs; and procedures for accelerated or conditional approvals of products have become increasingly important for cancer drugs – more so than for any other disease category.

The time that passes in the course of FDA review of INDs and NDAs is short relative to total R&D time (said to be 5-10 percent of total clinical development time), but FDA regulations govern much of what happens during the development and testing of new treatments by sponsors and in their preparation of documentation to meet FDA requirements (Hirschfeld and Pazdur, 2002). The duration of FDA review has decreased dramatically since 1992 with enactment of reforms mandated in the laws instituting user fees and changes allowing the provisional, accelerated approval of new drugs that reduce the amount of information required at the time of approval with the expectation that studies filling in the information base will be completed thereafter. These processes reflect the FDA's mission to protect the public's health by ensuring both safe and effective drugs and timely entry of those drugs into the market place and patient care.

History

As noted, new drugs may be sold in the United States only after they receive FDA approval -- based on adequate evidence that they are safe and effective in humans that is developed using study methods that meet criteria set out in FDA regulations. The FDA's authority derives from laws passed by the Congress. This includes mainly the Federal Food Drug and Cosmetic Act (FDCA) and its amendments, but others as well, such as the Public Health Service Act (dealing with biologics, among other things), the Federal Advisory Committee Act (which allows FDA to ask outside expert advice provided it is through properly chartered advisory committees), and other legislation that is significant, but narrower in scope.

The original Food and Drug Act of 1906 was enforced by FDA's precursor, the Bureau of Chemistry in the U. S. Department of Agriculture and was primarily concerned with misbranded and adulterated food and drugs in interstate commerce. The next major milestone, the FDCA was enacted in 1938. It only authorized the FDA to require evidence from sponsors that drugs were safe before they could be sold, but the Kefauver-Harris amendments of 1962 added a requirement for FDA pre-market approval with determination of both safety and efficacy on the basis of evidence provided by the sponsor. Currently, the Act requires that there be "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling…" (U.S. Food and Drug Administration, 1998). The Orphan Drug amendments to the FDCA in 1983 and three subsequent years provide special encouragement for development of drugs for uneconomic markets (usually dealing with a prevalence of less than 200,000 people in the United States). About 40 oncology drugs have been approved with orphan designation, but the program was not intended to address approval criteria or review times (Roberts and Hirschfeld, 2005). More recent amendments are described in greater detail below.

The FDCA (as amended) prescribes the basic framework for the approval of new drugs, and over the years a large body of regulation has been developed by the FDA that provides the details of how drugs may be tested and the standards of evidence to which drug sponsors will be held. FDA regulations have the force of law when, after going through prescribed steps that include input from all interested parties in a public process that often takes several years to complete, they are published in the *U.S. Code of Federal Regulations* (CFR). The FDA has been reorganized as medical technologies have changed. Traditionally, separate centers for drugs, biologics, and devices (as well as other centers that deal with foods and cosmetics) have taken responsibility for different types of products. The centers developed different practices and policies geared toward the products they regulated and the legislation and regulations that applied to them.

Most existing cancer therapeutics are drugs (small molecules) and have been evaluated through the Division of Oncology Products of the Center for Drug Evaluation and Research (CDER or its predecessors). Over the last decade or two, biological products have been developed to treat cancer and cancer-related conditions, and, as a result, the FDA officially transferred responsibility for therapeutic biologic agents from the Center for Biologics Evaluation and Research (CBER) to CDER beginning in January

2003, with the intention that all drug-like agents would be reviewed using the same criteria and by the same staff. CBER would retain authority over vaccines, blood cells, tissues, gene therapy and related products. The change was to involve no reductions in personnel, but would require the transfer of selected people and resources. As of 2005, the integration of the personnel and resources involved in biologics reviews is incomplete. The reviews are technically carried out within CDER, but by the same staff as previously. Their office remains segregated from the main CDER oncology staff. How well the new system is working to minimize the variability that previously existed between reviews carried out by CBER and CDER is not clear.

The shift of responsibility for most biologics to CDER would consolidate responsibility for most cancer products into CDER's Division of Oncology Products. Diagnostic tests for cancer are left in the Office of In Vitro Diagnostic Device Evaluation and Safety of the Center for Devices and Radiological Health (CDRH). One hope for newer agents is that evidence of specific activity at the molecular level will eventually be used to monitor treatment. However, these tests, although closely linked to the targeted agents themselves, would be regulated by a separate entity under the current organization. In view of progress in this direction and the likelihood that targeted agents will become more and more a reality, suggestions were recently made for further consolidation in cancer and even for FDA "selective approvals" contingent on post-marketing studies that enabled identification of subsets of cancer patients with molecular changes predicting response to treatment with specific targeted agents (Roberts and Chabner, 2004).

The Office of Oncology Drug Products (ODP)

Accordingly, in July 2004, FDA announced further changes to the agency's organization with the objective of strengthening review of products to diagnose, treat, and prevent cancer. These changes had been preceded by years of discussions with cancer advocacy organizations, industry representatives, and NCI about the need to consolidate oncology expertise across the agency,[15] and they followed several other changes FDA had recently made to cancer review, such as the formation of the FDA/NCI Interagency Oncology Task Force (see below) to enhance the efficiency of clinical research and the scientific evaluation of new cancer therapeutics.

Under the restructuring, a new Office of Oncology Drug Products (ODP) would oversee both traditional chemotherapies and biologically based treatments. The product scope also included hematologic therapies, radiation protection agents, medical imaging drugs, and radiographic agents used to diagnose, monitor, and treat cancer and other diseases. The rationale for the reorganization proposed that having all oncology products reviewed in one office could speed evaluation and promote the use of uniform scientific standards. However, it appears that cancer vaccines and cell-based therapies will remain in CBER and not be moved to ODP. The rationale for this policy is not clear in official FDA statements.

[15] www.fda.gov/bbs/topics/news/2004/NEW01091.html

ODP was placed in CDER, given that division's role in reviewing the majority of cancer products already, consolidating the three existing areas within CDER responsible for the review of drugs and therapeutic biologics used to diagnose, treat, and prevent cancer. The new ODP, therefore, would consist of three review divisions, although details are not final. Besides the drugs, the therapeutic biologic products included in ODP include recombinant therapeutic proteins and monoclonal antibodies.

FDA's goal with the creation of this new office is to improve consistency of review and policy toward oncology drugs, and bring together a critical mass of oncologists who will help develop new therapies. ODP will also provide technical consultation between CDER and other FDA components, including CBER, CDRH, and the Center for Food Safety and Applied Nutrition (CFSAN). The Director of the Office of Oncology Drug Products, although not yet named as of the beginning of 2005, will have the authority to approve totally new cancer products. Most other drugs (for example, new dosage forms or new indications) will be approved by the division directors within ODP.

To support ODP and coordinate work performed throughout the various FDA product Centers related to cancer, FDA also created an Oncology Program housed in ODP. The Oncology Program will facilitate the consultation of FDA experts across the agency, provide a forum to discuss and develop regulatory policy and standards, and serve as a focal point for agency interaction and collaboration with NCI and other important stakeholders. This program will also coordinate cross-cutting training and oncology educational activities and will include an agency wide Oncology Coordinating Committee to ensure consistent FDA policies for anticancer drug and biologics.

The reorganization will be implemented in the spring of 2005. It does not change the legal standards for approval of drugs or devices, but it is designed to help facilitate the ongoing development of new standards as practice and science evolve. Part of this new standard setting is expected to emerge from the FDA/NCI Oncology Task Force described below.

The IND Process

Before an investigational, or unapproved, drug can be given to any human, the sponsor must apply to the FDA for an investigational new drug (IND) exemption[16]. While developing the IND, sponsors are encouraged, though not required, to meet with the FDA. During such meetings, the sponsor can solicit FDA's views on the adequacy and interpretation of preclinical data and on clinical trial design. Pre-IND consultation improves the chances that the IND will be allowed. It is not binding on FDA during subsequent review of the development of the drug, but the special protocol assessment process described below does commit the FDA short of evident public health concerns. Furthermore, pre IND and end-of-phase II conferences have been shown to be associated

[16] The IND application actually seeks permission for an unapproved drug to be transported or distributed across state lines. This is usually necessary to get the drugs to clinical investigators; even if it is not necessary in early phase trials, it will be eventually, and current practice is for companies to file an IND before clinical testing of any new drug or biologic.

with shorter product development times compared to times of products that were not discussed (Roberts and Hirschfeld, 2005)

Before clinical testing, a sponsor must determine that a product is likely to have therapeutic benefit and establish that it will not expose humans to unreasonable risks when used in limited, early-stage studies. To this end, information is required in three broad areas:

1.) Animal pharmacology and toxicology studies -- preclinical data, evaluated to assess whether the product is reasonably safe for initial testing in humans, including: a pharmacological profile of the drug; information on the acute toxicity of the drug in at least two species of animals; short-term toxicity studies ranging from two weeks to three months, depending on the proposed duration of use of the substance in the proposed clinical studies; and also previous (for example, foreign) experience with the drug in humans;

2.) Manufacturing information -- information on the composition, manufacturer, stability, and controls used for making the product, evaluated to ensure that the company can produce and supply consistent batches of the drug;

3.) Clinical protocols and investigator information -- detailed protocols for proposed clinical studies to assess whether initial-phase trials will expose subjects to unnecessary risks, information on the qualifications of clinical investigators (professionals, generally physicians, who oversee the administration of the experimental compound), and commitments to obtain informed consent from the research participants, to obtain review of the study by an institutional review board (IRB), and to adhere to the IND regulations.

Of the three types of INDs, the Investigator IND is the one involved in bringing a new drug to market. The Emergency Use IND allows FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with the regulations. It is also used for patients who do not meet the criteria of an existing study protocol, or if there is no approved protocol. A Treatment IND is submitted to allow use of an unapproved, but promising, drug for serious or immediately life-threatening conditions in the final stages of formal clinical testing and FDA review. A fourth, "exploratory" IND is being considered by FDA (see the Critical Path section of this chapter). Once an investigator IND is submitted, the FDA has 30 days to review it and to notify the sponsor if it is determined that it cannot be approved. (http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm#Introduction)

The NDA/BLA Process

The NDA or BLA is the sponsor's formal proposal that the FDA approve a new pharmaceutical or biologic for sale and marketing in the United States. Technically, it is a proposal that FDA approve a claim about a drug not the drug itself. The data gathered during the animal studies and human clinical trials described in the IND become part of the NDA/BLA application. The goals of the NDA are to provide enough information to permit FDA reviewers to reach the following key decisions:

- Whether the drug is safe and effective in its proposed use(s) and whether the benefits of the drug outweigh the risks.

- Whether the drug's proposed labeling (package insert) is appropriate and what it should contain.

- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

An NDA/BLA requires documentation of all relevant information about the drug or biologic, including the results of all animal, laboratory, and clinical studies; and the product's chemical, biological and physical properties, and how it is manufactured, processed and packaged. From all this information, the FDA must be able to develop product labeling that defines the condition or conditions of use (specifying the patient population, as needed) and the appropriate doses and regimens.

The regulations that govern rules for approval state that safety and efficacy must be demonstrated by adequate and well-controlled trials. Safety and efficacy are not absolute values, however, and the general criterion for approval is evidence of a favorable risk-benefit profile. The general evaluation criteria used in oncology are

- improved survival,
- palliation of symptoms with no decrease in survival,
- protection against adverse events with no decrease in survival, or
- a reduction in the risk of developing cancer.

(Hirschfeld and Pazdur, 2002)

FDA staff with a range of technical expertise undertake an independent analysis of the clinical trial data. The final assessment balances the positive effects (benefits) of the agent against the toxicities and other adverse events (risks) reported according to their type, frequency, severity, duration, and clinical consequences.

The Oncologic Drugs Advisory Committee (ODAC)

The Oncologic Drugs Advisory Committee (ODAC) is a body of 12 non-governmental advisors serving staggered 4-year terms that provides independent external advice to FDA on approval decisions for oncologic drug NDAs. ODAC also has a statutorily mandated pediatric oncology subcommittee. In accordance with its charter, at least one member of ODAC is a patient representative, one a consumer representative, and one a statistician. Other experts are brought in to advise ODAC as called for by the task at hand. An ODAC meeting is usually called a few months after FDA receives an NDA and has conducted its initial analyses and shared them with ODAC, although not all

reviews for licensing applications are brought to ODAC. At the meetings, which are open to the public, both the sponsor and FDA present their findings to, and are queried by, ODAC members. After consideration and discussion of the evidence, ODAC votes on whether to advise approval. FDA is not bound by ODAC advice, but the agency usually follows it.

Evidence Required for Approval

As noted earlier, Congress amended the FDCA in 1962 to require for the first time that sponsors demonstrate the effectiveness in addition to the safety of their products through "substantial evidence" from "adequate and well-controlled investigations" before FDA could approve them for marketing. Since clinical trials are time-consuming and expensive, it is in both the public's and the sponsor's interest to conduct trials efficiently and quickly to develop "substantial" evidence through "adequate investigations."

Based on the 1962 amendment's legislative language and debates, FDA generally regards adequate and well-controlled investigations to mean at least two studies, each convincing, although at times a single excellent study accompanied by supporting evidence from studies of related questions (for example, a different dosage form, a different but related indication) has been deemed sufficient. This interpretation was codified in the FDA Modernization Act (FDAMA) of 1997 (section 115(a), amending section 505(d) of the FDCA), which states that, if so judged by the FDA, effectiveness may be established by "data from one adequate and well-controlled clinical investigation and confirmatory evidence" (U.S. Food and Drug Administration, 1998).

Before 1972, NIH's Bureau of Biologics was responsible for review of biologics and required a demonstration of "continued safety, purity, and potency" (as defined in the Public Health Services Act). Thereafter, the FDA assumed responsibility for review of the safety and effectiveness of biological products and approval of those agents has been held to the same standard as drugs: adequate and well-controlled studies. FDAMA reinforced this practice, directing the agency to take measures to "minimize differences in the review and approval" of biologic and drug products (U.S. Food and Drug Administration, 1998).

The Prescription Drug User Fee Act[17]

In the 1970s and 1980s, concerns were expressed by the pharmaceutical industry and sympathetic academics regarding the duration of FDA NDA reviews. The "drug lag" debate held that U.S. reviews were slower than those in the United Kingdom and certain European countries, and yet, faster times to market in such countries resulted in little evidence of harm and claims of greater benefit through earlier availability. The 1992 Prescription Drug User Fee Act (PDUFA) addressed that critique, not by relaxing any FDA regulatory requirements, but by responding to FDA's position that long review times resulted from insufficient funds to hire enough reviewers. PDUFA codified:

[17] This section is based on an unpublished manuscript by Richard Rettig, titled "The Implementation of the Prescription Drug User Fee Act of 1992 by the Food and Drug Administration."

industry acceptance of user fees on NDA and other submissions; FDA agreement to performance goals for reviews of applications; and congressional agreement that user fee revenue would not substitute for appropriations (and limitation of PDUFA legislative authority to 5 years). It was thus agreed that the funds supporting reviews could not fall below 1992 (later 1997) levels adjusted for inflation. This has had the effect, over time, of requiring resource shifting from other FDA activities.

Although, the idea of user fees was not new in the 1990s, by then both Congress and the pharmaceutical industry had begun to appreciate and accept FDA's position on increasing workload demands, both because of greater numbers and increased complexity of applications (Shulman and Kaitin, 1996). PDUFA was subsequently reauthorized in FDAMA ("PDUFA II") and again in the Public Health Security and Bioterrorism Preparedness and Response Act in 2002 ("PDUFA III"), with each reauthorization adding new goals and provisions. These laws authorized substantial fee collections, for example, the five year PDUFA III plan estimates receipts of a little over $1.25 billion total and FDA actually received approximately $825 million from drug and biologic manufacturers from fiscal years 1993 through 2001 (US GAO, .2002).

Performance Goals

User fees apply to prescription drugs, including most biologicals, and to over-the-counter (OTC) products that are the subject of an NDA. Exemptions include blood and blood products, in vitro diagnostics, other biologicals, and generic drugs. There are three types of fees: application fees, annual product fees, and annual establishment fees. Application fees apply to NDAs, Product License Applications (PLAs, required of biologicals), supplemental applications (for example, a new indication or labeling change), and prescription-to-OTC applications (Shulman and Kaitin, 1996).

In return for user fees, FDA agreed to certain performance goals, negotiated between the FDA Commissioner and the chairmen of the relevant congressional committees. PDUFA set performance goals for review times for both standard approvals and priority approvals, as follows:

- For *standard* NDAs and applications to add indications to the labeling (supplements) with clinical data, FDA agreed to review and act on 90 percent of such applications within twelve months from the date of submission. The current goal was set by PDUFA II, which amended this to 90 percent of such applications acted on within ten months. "Review and act on" meant that FDA would complete a comprehensive review of an application and issue an FDA action letter. An action letter might indicate approval, but it might also indicate deficiencies to be remedied, some potentially by more data or analyses, some not. Sponsor response to the agency action letter would restart the clock.

- For *priority* NDAs, PLAs, ELAs (Establishment Licensing Applications), NDA supplements and PLA and ELA amendments, the "review and act on" period was six months, and this has remained the goal through PDUFA II and PDUFA III. Drugs intended for use against serious and life-threatening illnesses, such as cancer, HIV/AIDS,

and Alzheimer's disease often fall into this priority category, but they must constitute a therapeutic advance to qualify for priority status.

- In cases where a major amendment to an application is submitted within three months of the anticipated FDA action date, an additional three months would be added to review time. This feature is intended to discourage filing an application for which additional important data are expected during the review period.

- Overdue applications and submissions were targeted for elimination within an 18 to 24 month period, depending on their nature.

- FDA agreed to establish a joint agency/industry working group to oversee efforts to improve review times; implement a project management system within twelve months for NDA reviews and within 18 months for PLA/ELA reviews; implement within CBER a performance tracking and monthly monitoring system similar to that in place in CDER; adopt uniform standards for computer-assisted NDAs in FY 1995; and initiate a pilot computer-assisted PLA program in FY 1993. FDA *review time* is defined by the agency as "the time it takes FDA to review a new drug application" (U.S. Food and Drug Administration). *Approval time* is defined as "the time from first NDA submission to NDA approval," and includes FDA review time for the first submission, plus any subsequent time during which a drug sponsor addresses the deficiencies in an NDA and resubmits the application, plus subsequent FDA review time. The median *review time* in months for priority NDAs fell from 16.3 months in 1993 to 6.2 months by 1997, to 6.1 months by 1999, and 6.0 thereafter (Table 2). Median *approval times* for priority NDAs fell from 20.5 months in 1993 to 6.4, 6.1, and 6.0 months for those same years.

For standard NDAs, median *review time* fell from 20.8 months in 1993 to 12.0 months in 1998 and thereafter; median total *approval time* fell from 26.9 months to 12.0, 13.8, 12.0, and 14.0 months for 1998 through 2001 (U.S. Food and Drug Administration).

Although the trend toward shorter review and approval times had begun before PDUFA -- approval times of 30-32 months on average for new molecular entities in the 1970s and 1980s had fallen to 24 months by 1990 (Temple, 1996) -- the continued, rapid decline is associated with implementation of PDUFA

Broader Impacts of PDUFA

The intent of PDUFA was to shorten product review and approval times, and times did become shorter. Furthermore, the salience of FDA's health promotion mission, that of getting good products to market and available to patients quickly, was enhanced relative to its consumer protection mission. The mission statement of FDA that became part of the language of FDAMA incorporated these two objectives, although over time questions have been raised whether the balance should have favored consumer protection to a greater extent or indeed whether "the FDA's first absolute priority is to protect the public health…" (Fontanarosa et al., 2004).

Table 2. APPROVAL TIMES FOR PRIORITY AND STANDARD NDAs CALENDAR YEARS 1993-2001

Calendar Year	Priority			Standard		
	Number Approved	Median FDA Review Time (months	Median Total Approval Time (months)	Number Approved	Median FDA Review Time (months)	Median Total Approval Time (months)
1993	19	16.3	20.5	51	20.8	26.9
1994	17	15.0	15.0	45	16.8	22.1
1995	15	6.0	6.0	67	16.2	18.7
1996	29	7.8	7.8	102	15.1	17.8
1997	20	6.2	6.4	101	14.7	15.0
1998	25	6.2	6.4	65	12.0	12.0
1999	28	6.1	6.1	55	12.0	13.8
2000	20	6.0	6.0	78	12.0	12.0
2001	10	6.0	6.0	56	12.0	14.0

SOURCE: FDA/Center for Drug Evaluation and Research
Last Updated: January 24, 2002

PDUFA also encouraged FDA relations with industry. With PDUFA came clear guidance from CDER leadership that the agency had an obligation to ensure that no more patients than needed were exposed to unapproved pharmaceuticals, and that working with industry to get clinical trials designed well was part of that obligation. PDUFA, then, encouraged a balancing of consumer protection and public health, on the one hand, and a more cooperative, science-based interaction with industry, on the other.

Special Protocol Assessments

Drug sponsors have complained about the lack of consistency by the FDA in communicating to sponsors about drugs from IND through NDA. For example, sponsors have claimed that studies allowed to proceed under INDs, even after repeated discussions with FDA regulatory staff, would be found inadequate in design or execution (even if done according to plan) when the work was complete and the NDA submitted. This was attributed to changes of personnel, and thus, opinions, over the several years that might elapse in drug development. Even though specifics of these cases have not been documented publicly, Congress recognized this as a potential problem and, in FDAMA {section 119(a)}, required FDA to establish a mechanism for prospective agreement on a

detailed study protocol (or at least particular aspects of it) that would—unless exceptional circumstances arose—form the basis for evaluating a product for approval and give sponsors the confidence to proceed knowing what was expected.

To address this problem, an FDA Guidance document for special protocol assessments was issued in May 2002 (Food and Drug Administration, 2002a). A special protocol assessment review can be requested by a sponsor for three types of studies. Although animal cancinogenicity and final product stability protocols are covered, the type most directly relevant to cancer drugs involves clinical protocols for phase III trials whose data will form the primary basis for an efficacy claim in an original NDA, BLA, or supplement when the trials had been the subject of discussion at an end-of-phase II/pre-phase III meeting with the FDA review division, or, in certain other instances, if the FDA was aware of the developmental context in which a protocol was being reviewed with a sponsor and questions answered.

Sponsors are required to submit their protocols before the anticipated start of the study (FDA recommends at least 90 days), allowing enough time to discuss and resolve issues. In applying for a special protocol assessment, the sponsor must identify the specific issues of concern, such as, sample size, study end points, choice of control group, methods for assessing outcomes, among others, and not simply submit the protocol by itself, since it is these specific issues that will be the focus of FDA's review and of the written agreement that emerges from the process. Under most circumstances, FDA has 45 days to complete the review.

The product of the review is clear documentation in writing of the areas of agreement and disagreement between the FDA and the sponsor on the key issues. The documentation can be in the form of a letter from FDA and/or the minutes of FDA-sponsor meetings. According to PDUFA: "…having agreed to the design, execution, and analyses proposed in protocol reviews under this process, the Agency will not later alter its perspective on the issues of design, execution, or analyses unless public health concerns unrecognized at the time of the protocol assessment under this process are evident." Furthermore, "(p)ersonal preferences of new individuals on either team (FDA or sponsor) should not affect any documented special protocol assessment." (Food and Drug Adminstration, 2002a).

Sponsors have been using the special protocol assessment process and publicizing its successful completion for particular products with some enthusiasm. (See, for example, http://www.exelixis.com/index.asp?secPage=arcrelease&rel=119, Monday, September 15, 2003)

Other Issues and Policies of Special Relevance to Oncology Drugs

Two oncology drug development issues have been of particular concern in the cancer community: the end points that are available for clinical trials, and the testing and approval of combinations of drugs, current and future.

There are no special rules for cancer (or cancer endpoints) in the laws that govern the approval of drugs or biological agents. These agents must meet the same basic evidentiary criteria for safety and efficacy as all other new drugs or biologicals. But the life-threatening nature of the disease and the relative paucity of effective treatments have led to somewhat different benefit-risk ratios for cancer and considerable pressure from drug sponsors and the public to speed approval. For example, between 1990 and 2002, more than half of all anti cancer drug approvals were based on end points short of survival (Johnson et al., 2003). This includes 34 out of 52 traditional approvals for anticancer drugs (including some for more than one indication) (Table 3). Tumor response rate and time-to-tumor-progression (TTP) have been the most commonly relied upon end points, depending on the assumption that improvements in those measurements eventually translate to increased survival times. These issues are discussed below.

Full Approval of Oncology Drugs

Until 1992, drug approval depended on a full, unconditional approval that was based on a direct demonstration of benefit to the patient. In the early 1980s, benefit was defined as either a longer life, a better life, or an established surrogate for one or both of these. Until the mid-1980s, FDA approved cancer drugs on the basis of a better tumor response rate (partial response, the proportion of tumors shrinking by defined degrees; or complete response, the disappearance of the tumor) that was better than the standard treatment. At that time, however, ODAC advised that tumor response was not a validated surrogate endpoint that reliably translated into worthwhile clinical benefit, particularly in light of the toxicity associated with treatment. FDA agreed and began requiring direct evidence of improvement in either survival or symptoms. Since then, FDA has moderated its position, allowing approvals on the basis of impressive improvements in tumor response rates. More recently, disease-free survival (the period between treatment and recurrence) was added to the acceptable end points, particularly for cancers in which most recurrences are symptomatic. The acceptability of a particular end point for full approval is judged on a case-by-case basis, depending on the type of cancer and its natural history and on how convincing the trial results are.

Currently, the end points that may lead to full approval are improved survival (primarily for cytotoxic drugs used as first-line therapy), disease-free survival (applying mainly to adjuvant trials), prolonged time to progression (mainly applied to hormonal or biological products), or palliation of cancer symptoms (usually in conjunction with tumor response). Response rate can be an adequate end point in rare but convincing cases, but it is usually considered as an additional end point, mainly in the case of some hormonal and biological agents. On its own, it can lead to conditional approval (Pazdur, 2000). No drug would be approved if it reduced survival, regardless of other positive effects (Hirschfeld and Pazdur, 2002). In all cases, if there is a standard treatment of demonstrated benefit to patients, the new treatment should be tested against it, to demonstrate either improved efficacy, or equivalent efficacy with a better safety profile. If there is no effective standard treatment, the control can consist of no treatment (usually best supportive care). Because cancer chemotherapy nearly always involves more than one drug, it often happens that a new drug replaces a drug in a known-effective regimen, or is added to a known-effective regimen.

Table 3: End points for oncology drug marketing applications, January 1, 1990-November 1, 2002

Drug (year, application type)	Indication	Approval Type	End Points Supporting Approval	Trial Design
Altretamine (1990, N)	Refractory ovarian cancer	Regular	RR	SAT
Altretinoin gel (1999, N)	Kaposi's sarcoma, cutaneous lesions	Regular	RR, cosmesis	RCT
Amifostine				
(1995, N)	To decrease cisplatin-induced renal toxicity in refractory ovarian cancer	Regular	Creatinine clearance, CR and TTP to assess potential tumor protection	RCT
(1996, S)	To decrease cisplatin-induced renal toxicity in lung cancer	AA	Creatinine clearance, RR to assess tumor protection	SAT
(1999, S)	To decrease xerostomia after radiation therapy for head and neck cancer	Regular	Salivary production and xerostomia scores	RCT
Anastrozole				
(1995, N)	Breast cancer, second-line treatment	Regular	RR, TTP	DB RCT
(2000, S)	Breast cancer, first-line treatment	Regular	RR, TTP	DB RCT
(2002, S)	Breast cancer, adjuvant therapy of postmenopausal patients with ER-positive tumors	AA	DFS	DB RCT
Arsenic trioxide (2000, N)	Acute promyelocytic leukemia, second-line treatment	Regular	CR and CR duration	SAT
Bexarotene capsules (1999, N)	Cutaneous T-cell lymphoma, skin lesions	Regular	RR, composite assessment of index lesion severity	SAT
Bexarotene gel (2000, N)	Cutaneous T-cell lymphoma, skin lesions	Regular	RR, composite assessment of index lesion severity	SAT
Bleomycin (1996, S)	Malignant pleural effusions	Regular	Recurrence of effusion	RCT
Busulfan injection (1999, S)	CML, conditioning regimen for stem-cell transplantation	Regular	DFS, time to engraftment	RCT
Capecitabine				
(1998, N)	Breast cancer, refractory	AA	RR	SAT
(2001, S)	Colon cancer, first-line treatment	Regular	Survival	RCT
(2001, S)	Breast cancer, with docetaxel after failed anthracycline treatment	Regular	Survival	RCT
Carboplatin (1991, S)	Ovarian cancer, first-line treatment	Regular	Pathologic CR, PFS, survival	RCT
Carmustine wafer (1996, N)	Recurrent glioblastoma multiforme	Regular	Survival	Placebo RCT
Cladribine (1993, N)	Hairy cell leukemia	Regular	CR and CR duration	SAT
Dexrazoxane (1995, N)	To decrease doxorubicin-induced cardiotoxicity	AA	Cardiotoxicity (clinical and MUGA scans), RR to assess potential tumor protection	Placebo RCT
Docetaxel				
(1996, N)	Breast cancer, second-line treatment	AA	RR	SAT
(1996, S)	Breast cancer, second-line treatment	Regular	RR, TTP, survival	RCT
(1999, S)	NSCLC, second-line treatment	Regular	TTP and survival	RCT
Epirubicin (1999, N)	Breast cancer, adjuvant treatment	Regular	DFS and survival	RCT
Exemestane (1999, N)	Breast cancer, second-line treatment	Regular	RR and TTP	DB RCT
Fludarabine (1991, N)	Refractory chronic lymphocytic leukemia	Regular	CR and PR, improvement in anemia and thrombocytopenia	SAT
Fulvestrant (2002, N)	Breast cancer, second-line treatment	Regular	RR and TTP	DB RCT
Gemcitabine				
(1996, N)	Pancreatic cancer	Regular	Survival, clinical benefit response (composite end point including pain, performance status, and weight gain)	RCT
(1998, S)	NSCLC	Regular	RR, TTP, survival	RCT
Gemtuzumab ozogamicin (2000, N)	Acute myelogenous leukemia, second-line treatment in elderly patients	AA	CR and CRp (CR with decreased platelets)	SAT
Idarubicin (1990, N)	Acute myelogenous leukemia	Regular	CR and survival	RCT
Imatinib mesylate				
(2001, N)	CML, blast phase, accelerated phase, and failing interferon	AA	Hematologic response and cytogenetic response	SAT
(2002, S)	Gastrointestinal stromal tumors (GISTs)	AA	RR	SAT
Irinotecan				
(1996, N)	Colon cancer, second-line treatment	AA	RR	SAT
(1998, S)	Colon cancer, second-line treatment	Regular	Survival	RCT
(2000, S)	Colon cancer, first-line treatment	Regular	Survival	RCT
Letrozole				
(1997, N)	Breast cancer, second-line treatment	Regular	RR, TTP	DB RCT
(2001, S)	Breast cancer, first-line treatment	Regular	RR, TTP	DB RCT
Leucovorin (1991, S)	In combination with FU for metastatic colon cancer	Regular	Survival	RCT
Liposomal cytarabine (1999, N)	lymphomatous meningitis	AA	Cytologic response	RCT
Liposomal daunorubicin (1996, N)	Kaposi's sarcoma	Regular	RR, TTP, cosmesis	RCT
Liposomal doxorubicin				
(1995, N)	Kaposi's sarcoma, second-line treatment	AA	RR	SAT
(1999, S)	Ovarian cancer, refractory	AA	RR	SAT
Methoxsalen (1999, N)	Cutaneous T-cell lymphoma, skin lesions	Regular	RR based on overall skin scores, improvement in edema and scaling, and fissure resolution	SAT

Drug (year, application type)	Indication	Approval Type	End Points Supporting Approval	Trial Design
Mitoxantrone (1996, S)	Patients with pain from hormone-refractory advanced prostate cancer	Regular	Decrease in pain	RCT
Oxaliplatin (2002, N)	Colon cancer progressing after bolus 5 FU/LV and irinotecan	AA	RR and TTP	RCT
Paclitaxel				
(1992, N)	Refractory ovarian cancer	Regular	Durable PRs in bulky tumors	SAT
(1994, S)	Breast cancer, second-line treatment	Regular	TTP	Dose-response RCT
(1997, S)	Kaposi's sarcoma	Regular	RR and clinical benefit (assessed by evaluating photographs)	SAT
(1998, S)	Ovarian, first-line	Regular	Survival	RCT
(1998, S)	NSCLC	Regular	TTP and survival	RCT
(1999, S)	Breast cancer, adjuvant therapy	Regular	DFS and survival	RCT
Pamidronate				
(1995, N)	Skeletal morbidity of osteolytic bone metastases of myeloma	Regular	SRE	Placebo RCT
(1996, S)	Skeletal morbidity of osteolytic bone metastases of breast cancer	Regular	SRE	Placebo RCT
Pentostatin				
(1991, N)	Hairy cell leukemia, second-line treatment	Regular	CR and CR duration, improvement in hemoglobin, WBC, platelets	SAT
(1993, S)	Hairy cell leukemia, first-line treatment	Regular	CR and CR duration	RCT
Porfimer sodium				
(1995, N)	For PDT in completely obstructed esophageal cancer	Regular	Luminal response and palliative response	SAT
(1998, S)	For PDT of CIS and microinvasive NSCLC	Regular	CR and CR duration	SAT
(1998, S)	For PDT of completely or partially obstructing endobronchial NSCLC	Regular	Luminal response and pulmonary symptom severity scale	RCT
Talc (1997, N)	To prevent recurrence of malignant pleural effusion	Regular	Recurrence of effusion	RCT
Tamoxifen				
(1990, S)	Node-negative breast cancer, adjuvant therapy	Regular	DFS	Placebo RCT
(1998, S)	To reduce the incidence of breast cancer in women at high risk	Regular	Occurrence of breast cancer	Placebo RCT
(2000, S)	To reduce the incidence of breast cancer after treatment of DCIS	Regular	Occurrence of breast cancer	Placebo RCT
Temozolomide (1999, N)	Anaplastic astrocytoma, refractory	AA	RR	SAT
Teniposide (1992, N)	Refractory childhood acute lymphoplastic leukemia	Regular	CR and CR duration	SAT
Topotecan				
(1996, N)	Ovarian cancer, second-line treatment	Regular	RR, TTP, survival	RCT
(1998, S)	Small cell lung cancer, second-line treatment	Regular	RR and response duration, symptom improvement	RCT
Toremifene (1997, N)	Breast cancer, first-line treatment	Regular	RR, TTP	RCT
Tretinoin (1995, N)	Acute promyelocytic leukemia, second-line treatment	Regular	CR	SAT
Vinorelbine (1994, N)	NSCLC	Regular	Survival	RCT
Zoledronic acid (2002, N)	Multiple myeloma and bone metastases from solid tumors	Regular	SRE	

Abbreviations: N, new drug application; RR, response rate; SAT, single-arm trial; RCT, randomized controlled trial; S, supplement; CR, complete response; TTP, time to progression; AA, accelerated approval; DB, double blind; ER, estrogen receptor; DFS, disease-free survival; CML, chronic myelogenous leukemia; PFS, progression-free survival; MUGA, multiple-gated acquisition; FU, fluorouracil; LV, leucovorin; PDT, photodynamic therapy; CIS, carcinoma-in-situ; NSCLC, non–small-cell lung cancer; DCIS, ductal carcinoma-in-situ; SRE, skeletal-related event.

Clinical trials designed to demonstrate improved survival are usually the most time-consuming and often require the largest numbers of patients. They nearly always require a randomized design, which is also true for trials designed to detect prolonged disease-free survival. Such trials, if large enough and with a long enough period of follow-up, can provide unambiguous evidence of benefit (although toxicities must be taken into account in the analysis). Survival need not be lengthened by years for a drug to be approved on that basis; often weeks or months will do (Justice, 1997).

TTP can serve as an end point if patients have measurable disease when starting to take the drug, and the objective is to inhibit the spread of the disease (measured by imaging studies). Although approvals based on TTP are considered full, not conditional, approvals, they do require the sponsor to follow patients and eventually report survival data. FDA has not approved drugs on the basis of a delay in cancer-related symptoms, but such evidence could fall within the scope of approval for delaying time to progression.

Response rate has figured in the full approvals of biological and hormonal products, including hormonal estrogen-receptor blockers and several aromatase (estrogen production) inhibitors, all for metastatic breast cancer. Complete responses (remissions) of clinically significant duration have been key to approval of other drugs, such as an agent for a rare form of leukemia, which produced complete remissions in the majority of patients (Justice, 1997). In general, the benefits of complete responses in hematological malignancies can be easier to appreciate since they may relieve bleeding or infections or the need for transfusions.

Partial responses (that is, decrease, but not disappearance, of the malignancy) are less likely than complete responses to be associated with an overall patient benefit (taking into account toxicities and the duration of response) and are much less likely to figure in full approvals. Approvals based on response rate generally require evidence of other benefit (such as palliation of symptoms) and require follow-up data to assure that survival has not been compromised.

End points intended as surrogates for survival (recurrence, progression, and response rate) have advantages in generally requiring smaller numbers of participants, regardless of trial design (because the number of definitive end points is larger) and because they can be completed more quickly. They can also be problematic to interpret because of the difficulties of standardizing measurement, because measurements occur at fixed points, and other ambiguities in quantitative determination of tumor size (or other disease measures).

Symptom control is an accepted end point as part of the evaluation for full approval of cancer drugs. Examples include a drug for pain control in men with hormone refractory prostate cancer and other agents for symptom control in small cell lung cancer, myeloma, and breast cancer, among others.

No cancer therapeutics have been approved thus far on the basis of a global quality of life measure, but they could be if the measures met certain criteria (for example, validation in the population and correlation with other disease-specific changes) and the benefit was considered to be of great enough value to patients. In general, for 90 separate claims from 1985 to 2003, approvals have usually been based on multiple end points, with response rate most frequent (60 percent of all claims and 75 percent of accelerated approvals), overall survival in 27 percent of all claims (only 5 percent as a sole end point), and time to tumor progression in 26 percent (Roberts and Hirschfeld, 2005).

Accelerated (Conditional) Approval

In response to pressure generated, as noted earlier, by the life threatening nature of cancer coupled with the paucity of effective treatments for this disease, Congress and the FDA developed measures to respond to the needs of sponsors, providers, and the public through legislation and regulations to allow faster approvals for new cancer drugs for which actual improvements in survival had not yet been shown. This kind of approval is conditional on the sponsor going forward with definitive post-marketing trials to demonstrate clinical benefit.

Preliminary measures to speed access to new drugs (Treatment INDs and parallel track/expanded access) had been tried for AIDS, but in 1992 FDA issued subpart H of its regulations for NDAs (21 CFR 314), a more formal solution that allowed sponsors to apply for accelerated approval for drugs that provide meaningful therapeutic benefit to patients over existing treatments (for example, ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy). Accelerated (or, as it was first named, conditional) approval may be granted on the basis of a surrogate endpoint(s) likely to predict clinical benefit such as various response rates, but definitive studies are supposed to be completed with due diligence for the approval to become final, assuming clinical benefit is confirmed. According to the preamble to the accelerated approval regulations, confirmatory trials would usually be under way at the time of the accelerated approval, although FDA has not required this, and it has not always been the case. If those trials are not completed or do not confirm a benefit, the FDA may exercise the option of accelerated withdrawal. However, when a confirmatory trial did not confirm a benefit (gefinitib), FDA did not withdraw the drug as noted below.

Between 1992 and 2003, 14 drugs for 19 cancer indications were granted conditional, accelerated approval. In early 2003, FDA and the Centers for Medicare and Medicaid Services (CMS) reviewed progress in completing the post-marketing, confirmatory trials for all of these drugs with ODAC. In four cases, the confirmatory trials had been completed and had led to full approval. Of the remaining drugs, eight that had received accelerated approval between 1995 and 2000 were reviewed with the following findings: a post-marketing trial was completed but was uninterpretable by FDA; the incidence of the indication being addressed by the drug (Kaposi's sarcoma in AIDS) had decreased substantially since the original trials, making patient recruitment difficult; the first confirmatory study was inconclusive, and a second was begun; and a number of trials were underway, but not completed. In none of these eight had trials been completed with analyzable data, and in some cases problems with design and patient recruitment remained (Cancer Letter, 2003). By mid 2004, updated figures were reported: only 6 of 23 "oncology related" accelerated approvals had received full approval. The same source also reported, that from the time of the first oncology accelerated approval in 1995, about one third of all cancer drug approvals were accelerated based on surrogate endpoints (Roberts and Chabner, 2004)

One observer has asked "…whether the accelerated approval mechanism enhances or hinders a sponsor's ability to complete definitive clinical trials with a new agent and, therefore, whether this regulatory strategy is in the best interest of cancer

patients" (Schilsky, 2003). Accelerated approvals may represent real treatment advances, but if studies are not completed, are inconclusive, or do not support the original evidence of efficacy, FDA may have a difficult time deciding on the appropriate action. At the ODAC meeting reviewing accelerated approval post-marketing trials, a senior FDA official commented that when a drug has proved active in a setting where nothing else had worked, it was not likely to be withdrawn because a post-marketing trial failed to show overall survival advantage (Cancer Letter, 2003).

In fact, as of 2005, FDA has never withdrawn a drug for lack of efficacy, only because of safety problems, and safety data available for drugs given accelerated approval have been sparse compared with data from regular approvals. Even after completion of post-marketing trials and full approval, some drugs originally granted accelerated approval had numbers of patients in their safety databases which were significantly smaller than numbers usually available when a cancer drug is granted regular traditional approval[18]. Those numbers, although probably sufficient to uncover common toxicities, may pose risks of missing rare toxic reactions (Schilsky, 2003). For example, three years following the full approval of one such drug (irinotecan) two large clinical trials were interrupted because of concerns of previously unrecognized thromboembolic toxicity and early death (Sargent et al., 2001). At present, there appears to be no real penalty if confirmatory studies are either not completed or show a lack of benefit, and the record suggests that considerable time may elapse before data are available for a decision in many instances. However, it should be noted that FDA and sponsor agreed to suspend marketing of one drug (gefitinib) in December 2004 when a phase III trial failed to confirm a survival benefit in lung cancer. Subsequently, use of the drug by clinical oncologists plummeted presumably because they were aware of the trial's results and were no longer prescribing it.

Testing and Approval of Drug Combinations for Cancer

The complexity of cancer has traditionally required the use of combinations of drugs with different mechanisms of action for most successful treatments. Also, the toxicity of most treatments and the ethics of testing against placebo in a potentially fatal disease have resulted in testing protocols that are more comparative with existing therapies than for drugs used in other diseases; therefore approvals are often based on comparatively better results in important health outcomes or lesser toxicity with equivalent survival or both. Treatment with a single conventional chemotherapy agent does not provide a durable cure, and this is likely to be so even for highly-targeted drugs.

The advent of new compounds more precisely targeted to specific molecular abnormalities of cancer cells, where activity against multiple targets may be required for effective results, poses additional new challenges to the drug developer and to regulatory agencies. Although qualitative and quantitative changes in molecular targets may be

[18] In fact, a subsequent review updated (but not significantly) the totals reported here and concluded that 62 percent of accelerated approval indications were based on trials of fewer than 200 patients and that safety data were often incomplete – Veronese, ML. Report card for accelerated FDA approval oncology drugs (1995-2003): is it time for a make-up test? - Accessed, 12/10/04 (and posted June 6, 2004) at http://www.oncolink.upenn.edu/custom_tags/print_article.cfm?Page=2&id+1087&Section=Conferences

measurable after a single targeted agent is given to patients, actual antitumor effects may not occur with a single agent and only be observed when multiple targets in the cancer pathway are affected by combinations of multiple targeted drugs or of newer targeted drugs with older cellular toxic drugs. And some new compounds may only suppress tumor growth but not necessarily cause tumor regression. When it comes to drug approvals, the end points appropriate for conventional chemotherapy agents may not be the most appropriate for some newer agents used in combination with other approved agents, or in combinations that involve more than one new agent. Research and development and regulatory difficulties posed by combination therapies in cancer are discussed below.

Approval of an Active Experimental Agent in a Combination, Where the other Agent(s) is a Licensed Product

It is not unusual for a new anticancer agent to be approved on the basis of activity in a combination regimen in pivotal trials[19] after the activity of the drug as a single agent has previously been demonstrated using the surrogate of tumor regression. A study design of the type A+B vs. A, where A is an approved agent and B is the experimental agent, may isolate the value of B and is therefore frequently used in pivotal trials. Other designs such as A+B versus A+C, where B is the only experimental agent have also been used. For example, in a trial of a new agent for advanced or metastatic non-small cell lung cancer, approval was based on a small survival advantage in an A+B vs A trial and an improved TTP and response rate (but no survival advantage) in the confirmatory A+B vs A+C trial (Eli Lilly and Company, 2003).

The monoclonal antibody targeted against the HER2 receptor in breast cancer was also approved (in February 2000) on the basis of the study design A+B vs. A (Genentech, 2003). In the pivotal trial, patients whose tumors over-expressed the HER2 protein and who had not previously been treated for metastatic disease, were randomized to chemotherapy with or without the new monoclonal antibody. In this case, the primary endpoint of the study was a statistically improved median TTP in the antibody containing arm of the trial. Subsequent data from the trial showed survival benefits.

Approval of Combinations of 2 (or more) Currently Unlicensed Products

Approval of two or more unlicensed products is governed by the general safety and efficacy provisions of the FDCA and FDA regulations. Although the FDA permits use of two or more investigational drugs in trials, the agency requires an evaluation of the effect of each drug individually, separate from the other drugs with which they are used, for approval of both drugs against cancer (Plaister, 2000) or other life threatening diseases (Food and Drug Administration, 2002c). When more than one investigational agent is included in a phase III pivotal trial, FDA recommends that the study design allow the contribution of an investigational agent to be distinguished (for example, through a factorial design). In any event, there are no clear examples in oncology where a

[19] "Pivotal" or "registration" trials are those phase III trials that provide data that a sponsor intends to use as the primary basis for NDA approval.

Table 4. Activity of oxaliplatin in combination with 5FU/leucovorin (LV) in colorectal cancer. Modified from (Sanofi-Synthelabo, 2002)

	Oxaliplatin + 5FU/LV	5FU/LV	Oxaliplatin
Number of patients	152	151	156
Response rate %	9	0	1
95% Confidence intervals	4.6-14.2%	0-2.4%	0.2-4.6%
Median TTP (months)	4.6	2.7	1.6
95% Confidence intervals	4.2-6.1	1.8-3.0	1.4-2.7

The P value for the comparison of response rate between the oxaliplatin plus 5FU leucovorin arm compared to the 5FU leucovorin arm was 0.0002.

combination of two unlicensed products has been approved for use together, although the issue arose for a particular combination in 1999 (Plaister, 2000) in the treatment of colorectal cancer. This controversy prompted congressional review, but subsequent discussions between the FDA and the company are not a matter of public record, and the application was withdrawn.

Approvals for an indication where the agent has no clinical activity in its own right

Despite the statement about the need for a drug to have activity in its own right, an important precedent was set by the approval of oxaliplatin in advanced colorectal cancer in August 2002. The basis for approval was a three-arm randomized trial comparing the drug alone against the drug plus standard therapy against standard therapy alone. An interim analysis of response rate and radiographic time to progression after 450 patients were enrolled in the study (Table 4) demonstrated that the drug had essentially no activity as a single agent in colorectal cancer, but in combination with standard therapy, it clearly enhanced the time to progression and response rate of patients. On this basis approval was granted.

At least two additional examples of compounds without intrinsic antitumor activity that have been combined with other agents have entered phase III trials, but neither turned out to have sufficient activity to warrant an NDA. However, it is reasonable to assume that the pivotal study designs were discussed and agreed with the FDA in advance (Levin et al, 2001, Von Pawel et al., 2000), and senior FDA oncology drug officials have commented publicly that there may be instances in which approval might rest on combination activity of a drug(s) inactive as a single agent(s).

Testing of combinations where both are unlicensed products

There are no regulations that prohibit the simultaneous evaluation of two experimental agents, and FDA is said to encourage such studies, as discussed above.

There are several precedents for such evaluations; for example, a phase I/II clinical trial of antibodies directed against the vascular endothelial growth factor receptor and the epidermal growth factor receptor (Mininberg et al., 2003). However, in practice, if two different sponsors are collaborating on such studies, there are likely to be a number of problems.

From a sponsor's regulatory compliance perspective these problems might include who is responsible for reporting of serious adverse events and other obligations associated with maintenance of the IND. Moreover, non-regulatory issues represent greater barriers to testing of new unlicensed combinations. These include concerns about intellectual property, costs, drug supply, and unanticipated adverse events. In addition, individual companies run clinical trials under a series of company-specific standard operating procedures (SOPs). Their databases are also likely to be incompatible. Agreeing on mutually acceptable SOPs and database access represent large problems for companies and should not be underestimated. In the example cited above, both compounds had the same sponsor. The paucity of other examples suggests that the barriers described above represent substantial hurdles to the simultaneous development of unlicensed agents with different sponsors.

Beyond Current Combinations

Unfortunately, there are few examples where the growth of a cancer cell is dependent on a single specific molecular rearrangement, and therefore the opportunities for specific and selective pharmacological intervention are limited. Although one therapy, imatinib (Gleevec®), has very successfully exploited the 9:22 chromosomal translocation (the Philadelphia chromosome) that occurs in a high proportion of patients with chronic myelogenous leukemia (Druker et al., 2001), in most cases there is substantial redundancy in biochemical pathways within the cancer cell so that pharmacological intervention in one pathway is compensated through other pathways or redundancy in that pathway (Petricoin et al., 2004).

Differences among cancer patients and different cancers in responsiveness and sensitivity to anticancer drugs pose additional problems. If patient populations and particular cancers more likely to respond to therapy and less likely to experience toxicity could be selected by prospective molecular profiling, this would represent a considerable advance in treatment. Pharmacodynamic studies are still in their infancy, but already significant difficulties have been identified including: choice of appropriate molecular endpoints and correlation of target effects with clinical benefits/ clinical trial designs and availability of clinical material for testing; assay selection and technical/quality assurance; and ethics, logistical issues, and regulatory considerations, among others.

In May 2002, the FDA and the Pharmaceutical Research and Manufacturers of America (PhRMA) jointly sponsored a workshop on pharmacogenetics in drug development and regulatory decision-making (Food and Drug Administration, 2002b). In March 2005, the FDA's policies on phamacogenomic data submissions by industry and on differentiating valid biomarkers and less well developed tests that are observational or exploratory were described in a guidance document intended to progress movement

toward individualized therapy.[20] Some of the potential regulatory implications of individualized therapy are illustrated by the following.

If a clinical trial assessed tumor expression of proteins 1 to 10, a reasonable strategy would be to treat each patient with drugs corresponding to those molecular targets aberrantly expressed by that patient's tumor. One patient might get two drugs and another might get seven drugs, and the two combinations might not overlap. This strategy might be in addition to, or compared against, standard therapy. In any case, decisions would be needed regarding which of all the drugs to consider for approval, or whether to treat them as fixed combinations for defined populations, how to identify appropriate molecularly categorized controls and to randomize, how to handle those drugs that have not been tested for, or found to show, individual anticancer activity; how to assess tumor growth suppression versus regression; among many others.

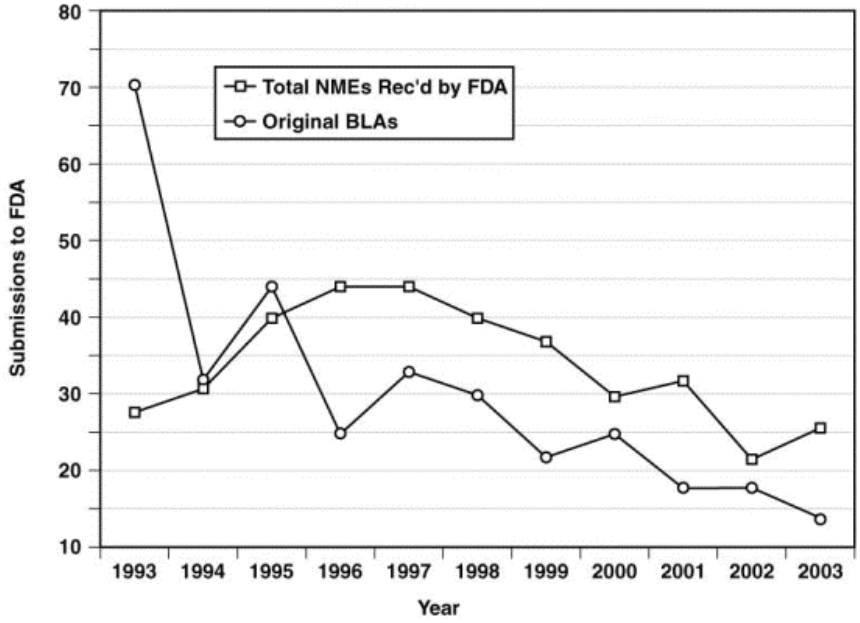
These are problems and questions that, given the current progress of cancer science, appear possible near-term challenges for both sponsors and regulators, although comments by FDA officials in various forums indicate that the agency understands and is prepared to think constructively about these issues. The FDA's approval of oxaliplatin also bodes well for its general flexibility in the future, but further thought on its position on the requirement for a drug to have activity in its own right and further careful identification and exploration of the kinds of issues discussed above, are going to be needed. Leveraging the resources of the NCI and FDA, through cooperation and coordination in such identification and exploration of issues (among others), appeared to the agencies to be a sensible approach and is described below through both informal and formal agreements.

The Critical Path Initiative

Most recently, the FDA has expressed a concern about the gap between the promise of new basic science in general and the development and use at the bedside of new priority drugs of all kinds (see Figure 1). In an attempt to improve evaluation of medical products and the speed and efficiency of review of new drugs, biologics, and devices, and at the same time strengthen evaluation of safety and effectiveness, the agency announced the Critical Path Initiative (Department of Health and Human Services, 2004). This initiative focuses on the critical path from discovery to medical product development to introduction through better safety assessment and evaluation of medical utility (effectiveness), and product industrialization. In collaboration with other agencies, industry and academia, the initiative addresses better evaluative (as opposed to basic or translational) science to develop the tool kit for evaluation of products and faster, less costly, and more predictable approvals. Extensive input was solicited in 2004 from interested parties and the public and a Critical Path Opportunities List is being developed with challenges and opportunities such as biomarkers, improved clinical trials, molecular imaging, data mining from FDA experience, and other possible science and technology

[20] Guidance for Industry Pharmacogenomic Data Submissions
http://www.fda.gov/cder/guidance/6400fnl.pdf

Figure 1. 10-year Trend in New Molecular Entity Drug and New Biological Product Submissions to FDA



that would help FDA and sponsors to move the evaluation process along in a more predictable and efficient way. Along these lines, FDA is considering adding an "exploratory" IND which would allow "phase 0" studies of a group of agents to look at proof of mechanism, receptor occupancy, early pharmacokinetics, and simplified procedures for screening in humans under limited circumstances at limited dosage before, but leading to, the usual investigator IND and phases I through III studies.[21] In this way, perhaps, agents more likely to succeed would enter the traditional development process making it less costly and more efficient. While not specific to cancer drugs, this initiative could improve their development and launch as well as drugs for other conditions although it is too early to know how successful it will be. As noted below, NCI has been supportive of the Initiative through the task force described next.

FDA and NCI Initiatives to Enhance Cancer Drug Development and Approval – The FDA/NCI Oncology Task Force

In May 2003, the Commissioner of the FDA and the NCI Director established the joint FDA/NCI Oncology Task Force "to enhance the efficiency of clinical research and the scientific evaluation of new cancer medications" (Barker, July 10, 2003 testimony http://www3.cancer.gov/legis/testimony/barker.html) and "to improve the development and availability of innovative medical products" (Mullin, July 10, 2003 testimony http://energycommerce.house.gov/108/Hearings/07102003hearing990/Mullin1578.htm). The Task Force adds another, more comprehensive, formal interagency agreement to those already in place (for example., the Cooperative Center for Biologics Evaluation and Review-NCI Microarray Program for the Quality Assurance of Cancer Therapies and

[21] http://www.toxforum.org/html/day_2.html

other Biological Products, and the FDA-NCI Clinical Proteomics Program), that are focused on specific programs. The new Task Force has a very broad agenda and, as noted above, could help in the ongoing development of new standards for FDA oncology drug review and approval as practice and science evolve.

This collaboration will provide FDA with exposure to state-of-the-art technology that will enable a better understanding of new products in development. NCI will benefit from hands-on experience with FDA's review process that should help guide research toward faster development of approvable products. Potential areas of collaboration include: joint training and fellowships; developing markers of clinical benefit, including surrogate endpoints; information technology infrastructure to better collect and share data; and ways to improve the drug development process. The first two initiatives announced in November 2003 are a joint cancer fellowship training program and the establishment of an electronic system to link and share data among cancer researchers from throughout the world. (Pam Holland-Moritz, Bioscience Technology, 1/5/04, http://www.biosciencetechnology.com/ShowPR.aspx?PUBCODE=090&ACCT=9000000100&ISSUE=0401&RELTYPE=RLSN&PRODCODE=00000000&PRODLETT=A).

The NCI-FDA Research and Regulatory Review Fellowship program is intended to give scientists interdisciplinary training to enhance proficiency in clinical research, regulatory approval processes, and the ability to translate clinical data into practical patient applications over a one to four year period. Fellows in the program at the M.D., Ph.D., or M.D./Ph.D. level train in clinical oncology programs at NCI and work in regulatory and review programs at the FDA. A primary goal of the collaboration is to provide cross-fertilization between the two agencies. This nationwide fellowship program accepts doctorate level fellows up to and including physicians who have completed their training and are board certified in medical oncology.

The plan to link cancer researchers to the FDA is intended to reduce the time needed to get new drugs reviewed for testing in clinical trials. It includes an electronic system for submitting INDs, created as part of the Cancer Biomedical Informatics Grid (caBIG) project. Uses of databases created through caBIG are expected to assist in dispersing and transferring basic oncology research and clinical trials information to cancer centers.

With NCI involvement, FDA has worked with the American Society of Clinical Oncology to identify biomarkers of clinical benefit as appropriate end points for cancer clinical trials by type of cancer and stage of disease. End points identified through this process will be published in FDA guidance documents. The Task Force may continue this work to identify clinically valid surrogate end points.

NCI and FDA will continue the current collaboration involving proteomics, that is, the discovery of protein markers in the blood that can be used to detect and monitor the progress of disease and drug response, and will also continue the Microarray Program for the Quality Assurance of Cancer Therapies, a program that has provided a foundation for the identification of new molecular targets, understanding of the mechanism of action

of targeted cancer therapeutics, and characterization of complex therapeutic cancer vaccines.

The Task Force plans to address the cancer bioinformatics infrastructure to streamline data collection, integration, and analysis for preclinical, pre-approval, and post-approval research across all of the sectors involved in the development and delivery of cancer therapies. The objective is to reduce the reporting burden for clinical investigators and improve the quality of reported data. Proposals under consideration include: creation of a shared repository for clinical investigator Curricula Vitae (CVs) to keep current and to eliminate the requirement of repeated submissions of such CVs; development of templates for INDs and clinical trial protocols to simplify the process of creating and submitting these documents and improve the quality of submissions. NCI grantees may also be product sponsors that FDA regulates. Given this dual role, there may be duplicative reporting requirements that can be streamlined through this collaborative effort.

Many of these collaborative efforts of the NCI and FDA also relate to the Critical Path Initiative such as a most recent gathering of industry, academia, advocates, and the two agencies to comprehensively review strategies to integrate biomarkers into clinical cancer trials. Also a subgroup of the Task Force is working on the development of biomarkers in coordination with the FDA's Critical Path Initiative, and a new subcommittee has been formed to examine the use of biomarkers to determine efficacy and long-term toxicity of agents in prevention trials (National Cancer Institute, 2005).

The New FDA Initiative to Speed Approvals

In early 2003, as part of the implementation of PDUFA III, the FDA announced an initiative to examine in three key areas the causes of delays in product approvals and find ways for the agency to reduce them (U.S. Food and Drug Administration). Two areas are of particular importance to cancer products: multiple review cycles for NDAs before they are approved; and guidance for preclinical and clinical product development, "to reduce uncertainty and increase efficiency for innovator product development." The third area, of general relevance to all types of products, is the institution of a continuous improvement/quality systems approach throughout premarket review.

Even though FDA is generally meeting its targets of 10 months for standard NDA reviews and six months for priority reviews, total approval times are often longer because NDAs fail to gain approval in a single cycle. CDER analyzed FDA experience with long review times for new molecular entity NDAs that were approved from January 2000 through either August 2001 (for priority reviews) or December 2001 (for standard reviews). Of approximately 30 NMEs undergoing standard review, 57 percent took longer than 12 months to be approved, ranging up to 54 months, and were almost evenly split between two and three review cycles. Approximately 15 NMEs had priority reviews, and 48 percent were approved in six months or less in one review cycle. Just less than half (46 percent) were approved in two cycles, and the rest were mostly approved in two cycles, although some took three cycles, the longest 54 months.

Failure to demonstrate safety (38 percent), concerns about efficacy (21 percent), manufacturing and labeling issues (14 percent each), chemistry, manufacturing and controls (10 percent) and general quality (3 percent) were the causes of prolonged standard reviews. Chemistry, manufacturing, and controls issues (46 percent), followed by safety (27 percent), efficacy (18 percent), and manufacturing (9 percent) made up the causes for prolonged priority reviews. A similar, but less comprehensive, study of biologics products by CBER found that the primary reasons for delayed approval related to major changes in product manufacturing (7 of 11 BLAs), and the rest related to efficacy and safety. Although analyses involved relatively small numbers of products, they appeared to rule out FDA procedures as the cause of delay. However, they suggested to the FDA that problems could be reduced through clearer guidance and improved communication to sponsors.

Guidance documents represent an important FDA communication device to companies and other sponsors. Under the new FDA initiative to speed approvals, the Center for Oncology Drug Products is undertaking to produce better guidance for oncology products on key topics and has been in discussion with the American Society of Clinical Oncology about appropriate endpoints for cancer clinical trials, as well as developing other documents within the agency.

Several hundred current FDA guidance documents address a wide range of topics, including several dozen related to cancer. Guidance documents do not have the force of law or regulation, nor do they legally bind FDA or drug sponsors. But they do communicate the agency's current thinking on a subject, and FDA employees are generally expected to adhere to them. FDA defines guidance documents as those prepared for FDA staff, applicants/sponsors, and the public that describe the agency interpretation of, or policy on, regulatory issues such as design, production, labeling, promotion, manufacturing, and testing of regulated products; the processing, content, and evaluation or approval of submissions; and inspection and enforcement (21 CFR 10.115).

Procedures for developing guidance documents had been reviewed and amended in provisions of FDAMA and more formally described in an updated regulation (21 CFR 10.115), effective October 2000. The regulation created two categories of guidance. Level 1 guidance documents are for new or changed interpretations of statutes or regulations and for more complex or controversial issues. They follow a notice and comment procedure, with initial publication of a draft on the Internet, followed by preparation of a final version for Internet availability. A notice in the *Federal Register* announces the document. This process can involve more than one round of review and comment and may take years for controversial subject matter. Level 2 documents explain existing practices or minor changes in interpretation and are prepared by FDA, with input and involvement from inside and outside FDA, as deemed appropriate. They are then posted on the Internet and implemented immediately.

Guidance documents are of great importance because FDA staff are restricted in ways they can convey this kind of information to their constituencies. According to 21 CFR 10.115, "The agency may not use documents or other means of communication that are excluded from the definition of guidance document to informally communicate new

or different regulatory expectations to a broad public audience for the first time." In meetings with drug sponsors about specific products, FDA staff may discuss regulatory requirements, but guidance documents are otherwise the main sources of information.

Summary of the FDA Role

The FDA strongly influences drug development and marketing, mostly toward the end of the process. Drug discovery, early development and some preclinical work is largely unaffected by the legal requirements that FDA enforces, and is much more dependent on decisions taken by drug developers and the state-of-the-art of cancer science. The FDA's influence becomes increasingly critical as information is developed specifically for an IND submission and is felt most during the period of clinical studies and the preparation of an NDA or BLA.

The means available to FDA to allow the drug development and approval process to proceed efficiently involve streamlining internal procedures and making sure that sponsors are able to streamline their research and development to produce what is needed in a form that meets the evidentiary standards of the laws and regulations that FDA is charged with carrying out. Changing the standards themselves is a Congressional prerogative. The Congress has kept a close watch on the FDA, and has enacted legislation (for example, through FDAMA and PDUFA, as mentioned several times in this chapter) facilitating accelerated approval, expedited reviews, and other innovations that have allowed the agency to speed the drug development and approval process. FDA itself has taken steps to improve reviews and approvals and implement cancer specific changes, such as moving toward providing a single cancer focus in the agency.

4

SUMMARY: THE ROLES OF THE NCI AND FDA IN DEVELOPING ANTICANCER AGENTS

NCI has played, and should continue to play, an important role in the development of new cancer therapeutics. That role has changed and will continue to evolve as the basic science underlying cancer and the development of agents to fight cancer evolve. That is NCI's challenge: to continue to fill gaps and catalyze new fields, both on its own and in collaboration with other agencies, academia, and industry. This may involve initiating new programs and phasing out others, a process that has gone on for decades at NCI, both on its own initiative and pursuant to congressional directives. In defining its role, then, in the development of new cancer therapeutics, NCI may variably emphasize basic science and discovery of new agents or development and introduction of agents of others in coordination with FDA.

For NCI, adapting to new science and a changing mix of actors has meant: modifying drug screens and developing new *in vitro* and *in vivo* models; exploring more effective toxicologic evaluations; reviewing the organization of clinical trials; setting up compound repositories; providing support to academic and other drug developers; a recent emphasis on fields of molecular targeting, biomarkers, genomics, proteomics, assays and databases of genetic changes in cancer; working more closely with industry; and an array of research supports; among others; and, in general, balancing its cancer research roles with responsibilities to encourage quality cancer care and advances in therapeutics. The role of the NCI in developing new therapeutics for cancer is not as precisely defined in statute and regulation as is that of the FDA. It is unarguable, however, that, as a research agency, NCI, with congressional support, needs to continue to advance the basic and clinical cancer science that is the foundation of new and better cancer therapeutics.

FDA has been responsible for review and approval of cancer therapeutics in the United States as defined in the statutes reviewed in this background paper, and on its own and at congressional directive has made changes in its procedures and internal structure to improve the efficiency of reviews and approvals and communications to drug and biologics sponsors.

For FDA, this has meant: meeting the legal requirements for assessing safety and efficacy of all drugs, including cancer drugs, and for all biologics, including cancer biologics when this responsibility was transferred from NIH; developing evaluative science and the evaluation criteria for cancer drugs and performance goals for reviews and approvals; improving communications and guidance documents for sponsors; developing policies for accelerated approvals and post-marketing confirmatory trials of cancer drugs and appropriate endpoints for cancer trials and approvals; exploring and openly discussing ways of approaching trials, reviews, and approvals of combinations of cancer drugs; thinking through problems and solutions relevant to more precisely molecularly targeted drugs and approaches to cancer and populations with identified

genetic changes; implementing organizational changes to emphasize and focus on cancer therapeutics; among others; and, in general, balancing its role as a consumer protection agency with its obligation to make useful medications available to the marketplace and patient care on a timely basis.

Both agencies are responding to the promise and challenges posed by advances in basic and clinical science in cancer and related fields and the need to adjust strategies and programs to this progress in scientific understanding.

Both agencies have issued statements and taken steps to coordinate, collaborate, and cooperate with the objective of ensuring that the potential of recent and projected scientific progress in cancer is translated to new anticancer therapeutics that are less toxic, more specific to precise molecular targets, and more effective in tumor control. NCI and FDA collaborations and continuing work to update procedures and policies for drug identification and development appear to be encouraging directions for the future. The information reviewed in this background paper, however, suggests that scientific, procedural, and policy problems remain that will require continuing effort from these agencies, singly and in concert, if their goals in the fight against cancer are to be realized in the most efficient and effective directions.

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ACRONYMS AND ABBREVIATIONS

BDP	Biopharmaceutical Development Program
BLA	Biologics License Application
BRM	Biological Response Modifier
CBER	Center for Biologics Evaluation and Research
CCNSC	Cancer Chemotherapy National Service Center
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	U.S. Code of Federal Regulations
CFSAN	Center for Food Safety and Applied Nutrition
CGAP	Cancer Genome Anatomy Project
CMS	Centers for Medicare and Medicaid Services
DCTD	Division of Cancer Treatment and Diagnosis
DNA	Deoxyribonucleic acid
DTP	Developmental Therapeutics Program
EDRN	Early Detection Research Network
ELA	Establishment Licensing Application
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act of 1997
FDCA	Food, Drug, and Cosmetic Act of 1938
FLAIR	Flexible System to Advance Innovative Research
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
LMT	Laboratory of Molecular Technology
NCAB	National Cancer Advisory Board
NCCN	National Comprehensive Cancer Network
NCDDG	National Cooperative Drug Discovery Group Program
NDA	New Drug Application
NIH	National Institutes of Health
NME	New Molecular Entity
ODAC	Oncologic Drugs Advisory Board
ODP	Office of Oncology Drug Products
OTC	Over-the-Counter (non-prescription) drug
PDUFA	Prescription Drug User Fee Act of 1992
PhRMA	Pharmaceutical Research and Manufacturers of America
PLA	Product License Application
RAID	Rapid Access to Intervention Development Program
RAMEM	Radiation Modifier Evaluation Module Program
RAND	Rapid Access to NCI Discovery Resources Program
RFA	Request for Applications
RNA	Ribonucleic Acid
SAGE	Serial Analysis of Gene Expression
SPORE	Specialized Program of Research Excellence
TTP	Time to progression